X-RAY STRUCTURAL STUDIES OF ANTIBIOTIC MATERIALS

BY

RICHARD JAMES GIRVEN M.Sc.(N.Z.)

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My greatest appreciation must be for the patience and encouragement of my wife Jean, and for her devoted support during this work.

DECLARATION

The work described in this thesis was carried out in the School of Mathematical Sciences, Plymouth Polytechnic, under the supervision of Dr. M. O. Boles.

This is to certify that the work described in this thesis has been performed by Mr. R. J. Girven under my supervision during the years 1973 - 1976.

M. O. Boles.

Dr. M. O. Boles,
Senior Lecturer,
School of Mathematical Sciences,
Plymouth Polytechnic,
Plymouth.

ABSTRACT

Optimum conditions were devised for the crystallisation of a number of antibiotics of pharmaceutical interest, and related compounds of particular significance in structure activity investigations. Single crystal X-ray analysis techniques were then used for the determination of the structures of two β- lactam compounds and an analgesic compound of unusually low physical dependence liability.

The molecular parameters determined for these compounds are discussed in terms of their relationship to analogous compounds, and in the context of accepted views regarding structure activity relationships. The three compounds studied in detail are:-

(i) Benzyl 6α-benzyl 6β-isocyanopenicillanate.

This compound is an intermediate in a synthetic route for preparation of 6- di- substituted penicillins.

There has been considerable recent work in this area of penicillin chemistry, following the discovery of an active naturally occurring 6α-methoxy cephalosporin, and a brief survey of the synthetic routes is included in the appendix section. The structure determination of the title compound was done for the purpose of establishing the configuration of the 6-benzyl substituent.

(ii) (3R, 4R)-1-(1-benzyloxycarbonyl-2-methyl-prop-1-enyl 4 - (βmethylallylthio)-3-triphenylmethylamino) azetidin-2-one.

Monocyclic lactams have attracted interest because of the antibiotic activity of several groups of compounds, particularly the nocardicins, which contain an oxime function in the 3-substituent. Seco penicillins, which are derived from penicillins by alkylative cleavage of the 1-2 bond, have no antibiotic activity but are of theoretical interest since the reduced strain in the bonding about the

ring nitrogen should allow greater lactam resonance stabilization than is possible in fused ring compounds. The relevant bond lengths and interatomic angles are discussed with reference to the results of other workers.

(iii) Anidoxime:- O-(4-methoxyphenylcarbamoyl-3-diethylaminopropiophenone oxime hydrochloride.

The pharmacological properties of this non-narcotic analgesic differ so widely from those of other analgesics, that its structure is of special interest. The chemical significance and pharmacological properties of anidoxime are discussed with reference to established analgesics, with known structure activity relationships.

CHAPTER 1

INTRODUCTION

Bioactivity of organic compounds may be determined by numerous factors, of which some appear to be associated with overall molecular size and shape, while others are related to the reactivity of particular functional groups, and their relative orientation. Investigation of the detailed structural features of bioactive compounds therefore requires determination of interatomic distances, bond angles, substituent configuration, and ring system conformation.

In many instances the usual physico-chemical techniques, for example absorption spectroscopy and nuclear magnetic resonance, yield conclusive evidence for structural assignment, when this evidence is considered in relation to the known structure of synthetic precursors, and established reaction pathways. Frequently, however alternative product configurations are available, as in compounds which are formed via carbonium ion intermediates, and configurational assignment is not always possible from chemical evidence. Steric requirements, or the energetically favoured overlap of π orbitals for charge delocalization may determine which of several conformations is adopted by a non aromatic fused ring system. The importance of steric factors is often evident from the large differences in observed potency between enantiomers, diasterisomers, or conformational isomers of many bioactive compounds.

The detailed three dimensional structure of a compound and the packing arrangement in the solid state, may usually be determined by X-ray crystallography, provided that single crystals of adequate size and quality are available. The first section of this work concerns the crystallisation of a number of compounds and in this chapter, a description of the techniques used is followed by a summary of the results for individual compounds. The determination of the crystal structures of three of these compounds is described in chapters 3 - 5.

1.1 Crystallisation Techniques

Crystallisation of an organic compound from solution is usually achieved either by slowly cooling a hot concentrated solution until the saturation concentration is exceeded, or by evaporation of solvent from an unsaturated solution at room temperature. A few compounds display a negative solubility vs - temperature curve, and an example, ampicillin anhydrate, is discussed below. Crystallisation is sometimes inhibited by formation of stable supersaturated solutions, particularly from compounds with high solubility at room temperature.

1.2 Solvent Selection

The choice of solvent for ionic compounds, for example, hydrochlorides of organic bases, or alkali metal salts of carboxylic acids is severely restricted. Water is almost always necessarily the major component of any solvent combination, and the only practical organic solvents which are sufficiently miscible with water are the lower alcohols, acetone and tetrahydrofuran. Solvent selection for compounds which are covalent, or essentially undissociated, is less restricted, and it is frequently possible to grow crystals from several solvents or combinations of solvents. For this reason, a systematic solubility investigation is necessary when the supply of a compound is limited to 1 - 2g.

1.3 Solubility and Crystallisation trials

The solubility of a compound in ethanol, isopropanol, acetone, ethyl acetate, chloroform and cyclohexane may be ascertained from small scale experiments. Initially 10 mg of compound is warmed with 0.20 ml of a solvent in a 2 ml vial. Further additions of 0.20 ml solvent are made until a clear solution is obtained upon warming. The vial is then allowed to cool in air and any crystals which form are examined with a magnifier, through the wall of the vial. Should significant crystal-

lisation occur the solid is redissolved by heating, and the solution cooled more slowly by standing the vial in a 20 ml vial containing 10 ml water at a temperature below the boiling point of the solvent. Crystal size is generally larger when a solution cools slowly. If crystal quality is good, but recovery is low, the procedure may be repeated, using a higher concentration of the compound, or alternatively, further trials may be carried out using solvent combinations. The crystals initially formed from the single solvent are redissolved by heating, and the hot solution is diluted with a miscible solvent in which the compound is only slightly soluble. The second solvent must be added slowly, or should be pre-warmed to avoid precipitation, the onset of which is signalled by a cloudiness in the solution which will not clear on heating. When the compound has initially been dissolved in acetone, or alcohols, the added solvent may be ethyl acetate or water. If the initial solution is in chloroform, dichloromethane or ethyl acetate, the added solvent may typically be heptane, cyclohexane, or petroleum ether. The temperature of the initial solution should not be above the boiling point of the solvent added, and it is preferable to add a solvent of higher boiling point than the initial solvent. For example, cyclohexane, rather than ether or a low boiling petroleum ether, should be used when diluting a chloroform or dichloromethane solution. Crystallisation by evaporation requires that the solution gradually becomes saturated by loss of the stronger solvent.

The above selection procedure may indicate several reasonable systems from which a choice is made on the basis of crystal size, quality, or habit. A scaled up crystallisation is then attempted, using 100 - 200 mg of compound, in a 20 ml Erlenmeyer flask, and allowing the solution to cool very slowly, by clamping the flask in a container of 600 ml water at 40 - 50^{o}C. The mouth of the flask is loosely covered to retard evaporation, and prevent the entry of dust. A compound may

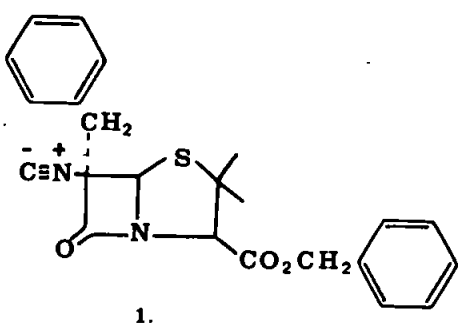
be found to dissolve easily in ethyl acetate, dried acetone, absolute ethanol, or tetrahydrofuran, but the solution remains cloudy, however dilute. This can result from entrainment of traces of sodium chloride or sodium sulphate in the compound during extraction and drying procedures. Filtration through celite may be necessary, or alternatively, the addition of a trace of water, may yield a clear solution, which retains the inorganic impurities during crystallisation of the organic compound. The method requires that the added water dissolves completely, and is of no value for solvents or solvent mixtures which are immiscible with water. Certain compounds crystallise as hydrates, and rigorously dried hygroscopic solvents may inhibit crystallisation.

1.4 Crystal Measurements

Interfacial angles, of the crystals described in the next section were measured, using a microscope with a rotatable stage calibrated in 1^{o} intervals. Indices were assigned to crystal faces on the basis of agreement between observed angles and those calculated from unit cell parameters. The crystal drawings in this chapter are clinographic projections, and crystal photographs were obtained using a Zeiss Tessovar.

1.5 Individual Compounds

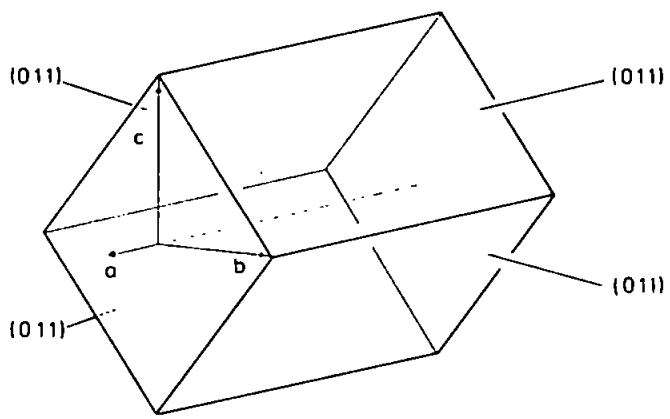
(i) Benzyl 6α - benzyl 6β - isocyanopenicillanate (Ref BRL 11827)

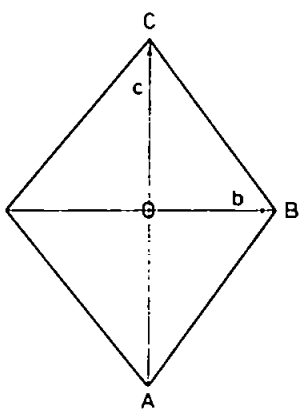


1.

PLATE 1: Benzyl 6α -benzyl 6 β-isocyanopenicillanate

Crystals from chloroform-cyclohexane ... ...





$\angle OBC = 1/2 \angle ABC$

$= \tan^{-1} c/b$

$= 52 \cdot 46^{\circ}$ calc.

$(52 \cdot 2 \pm 5^{\circ}$ obs.)

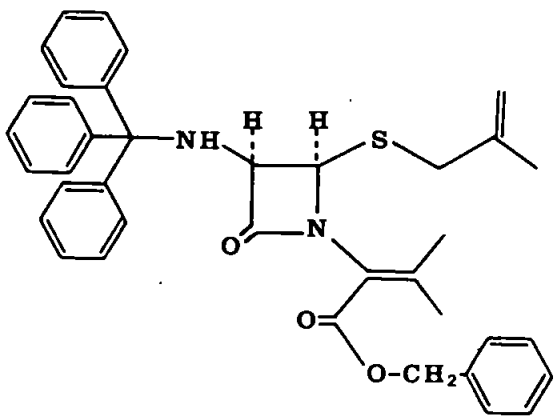
Fig. 1·1 – CRYSTAL INDICES OF ISOCYANOPENICILLANATE

BRL-11827

Slow evaporation over a period of several days of a solution of 0.5 g penicillanate 1, in 5 ml chloroform diluted with 30 ml cyclohexane, yielded clusters of slender white needles of striated appearance. Some crystals were over 1.5 cm in length, but microscopic examination showed that many were composites of parallel individuals. Typical crystals, as illustrated in Plate 1, showed prism faces $\{011\}$, but lacked well defined terminal faces. The crystal geometry is illustrated in Fig 1.1.

Although the compound was reasonably stable, it was gradually converted to the 6β- amino analogue, in the solid state or in solution, probably by absorption of traces of water and acidic contaminants from the atmosphere. The amine was identified by thin layer chromatography in petrol-ethylacetate 1 : 1, and since it is less soluble in chloroform than the isocyano compound, but more soluble in water, purification was achieved by rapidly extracting a chloroform solution with ice-water. The crystal structure determination is described in detail in Chapter 3.

(ii) (3R, 4R) - 1 - (1 - benzyloxycarbonyl - 2 - methyl - prop - 1 - enyl) - 4 - (β - methylallylthio) - 3 - (triphenyl - methylamino) - azetidin - 2 - one. (Ref EB 976)



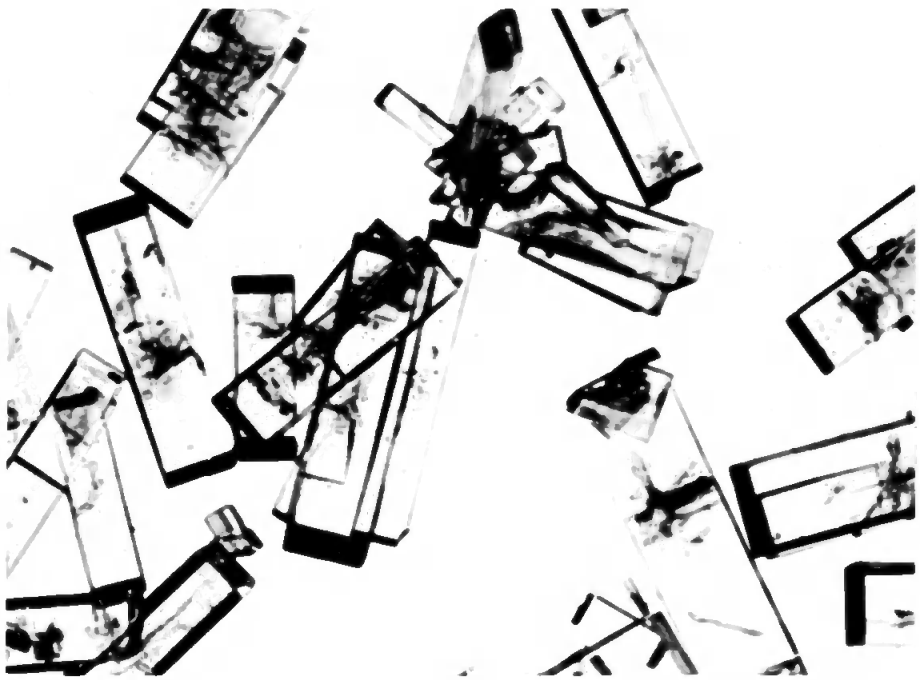
2.

The purified seco-penicillin, supplied in powder form by Beecham Pharmaceuticals, was soluble in ethanol, isopropanol, acetone, ethyl

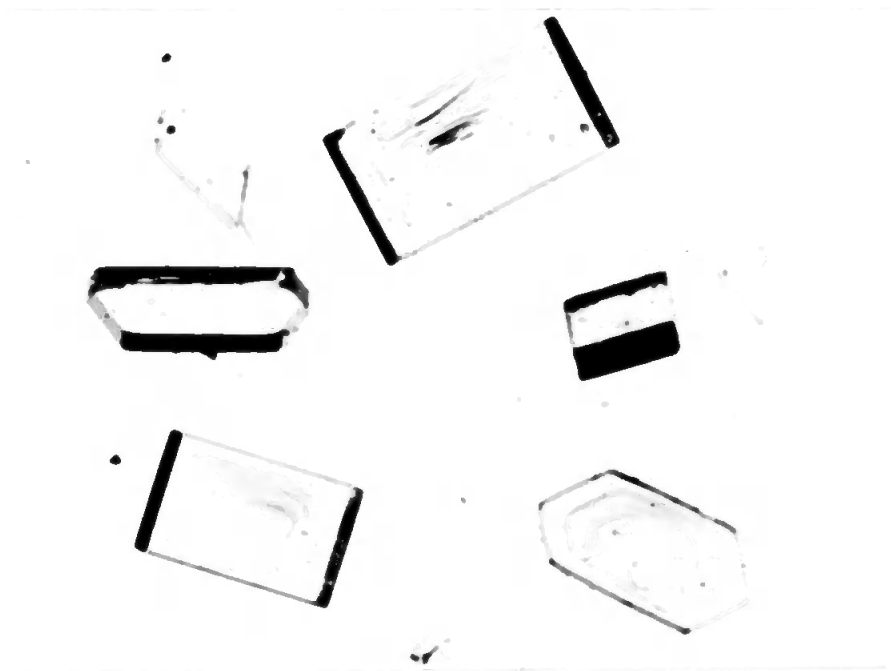
PLATE 2: The seco penicillin E.B. 976

(a) Crystals from acetone water ... ...

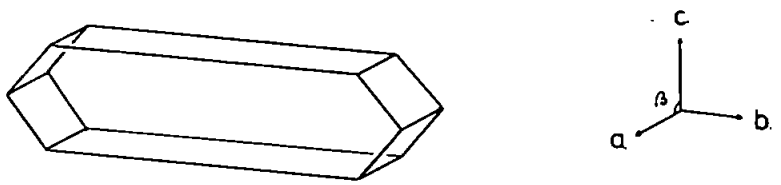
(b) Crystals from ethyl acetate-acetone water ...



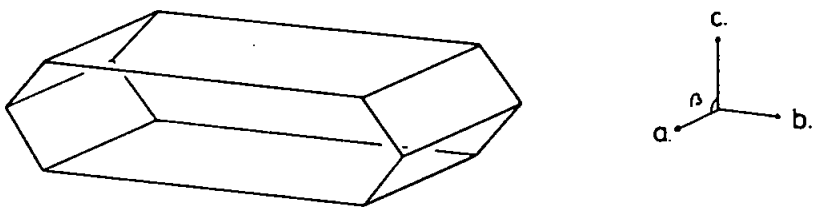
2a



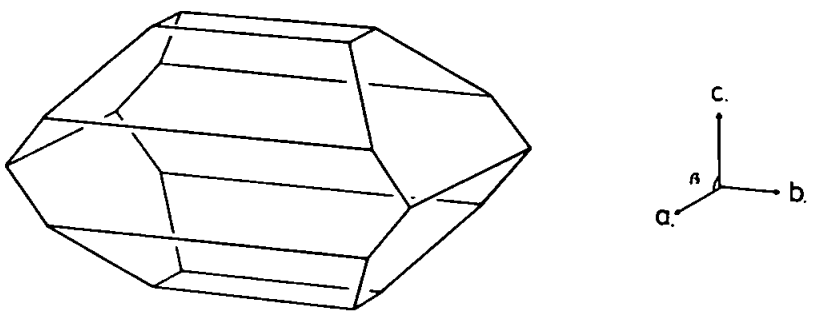
2b



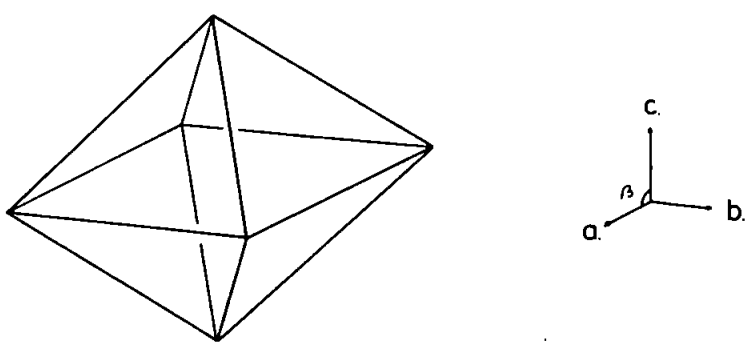
a.– acetone water



b.– ethyl acetate-acetone-water



c.– chloroform heptane, 1st crop



d.– chloroform heptane, 2nd crop

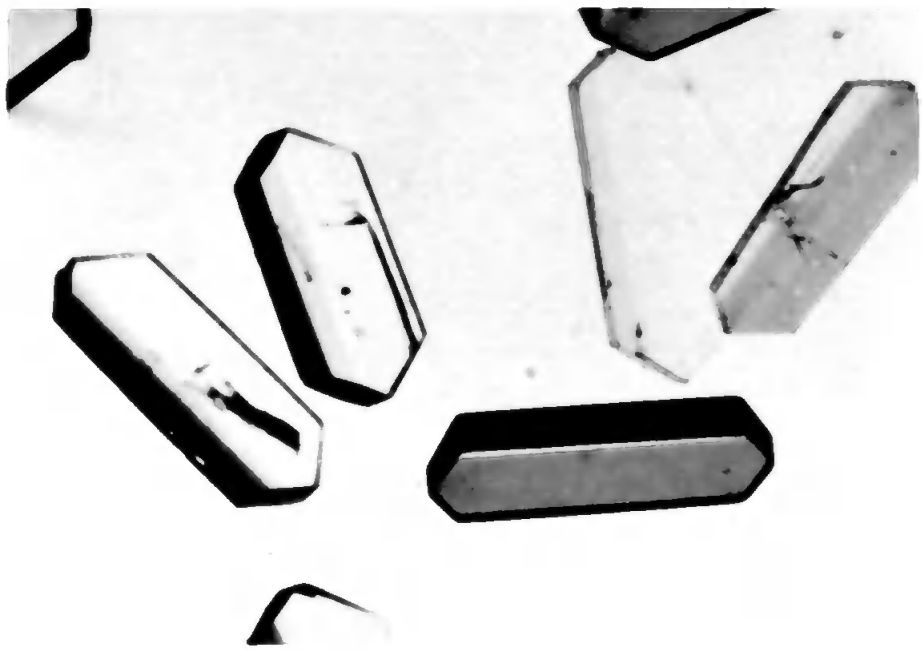
Fig 1·2–Solvent dependence of crystal habit of seco penicillin

EB-976

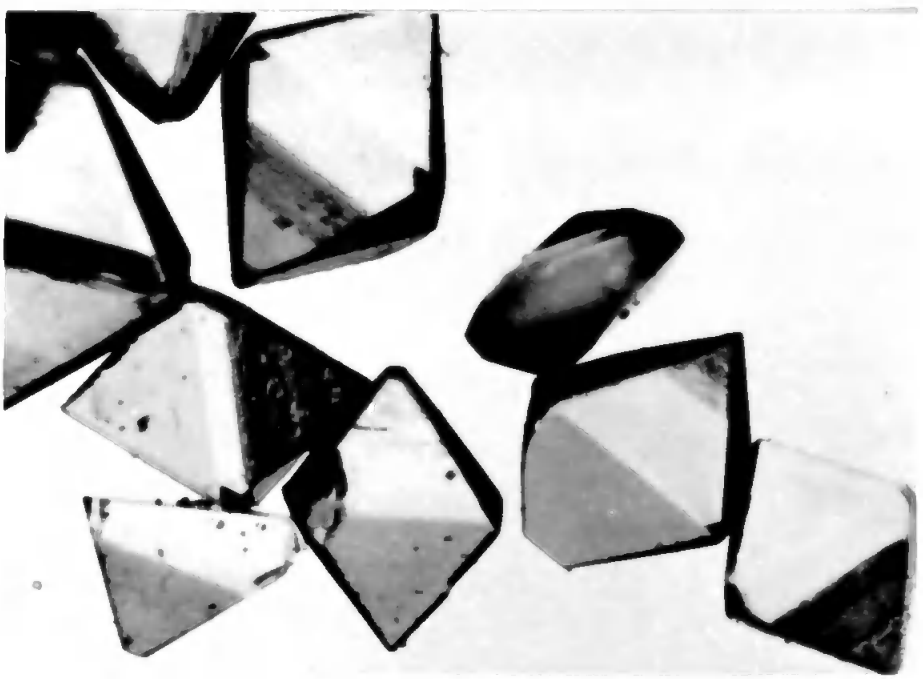
PLATE 3: The seco penicillin E.B. 976

(a) First crop crystals from chloroform heptane ...

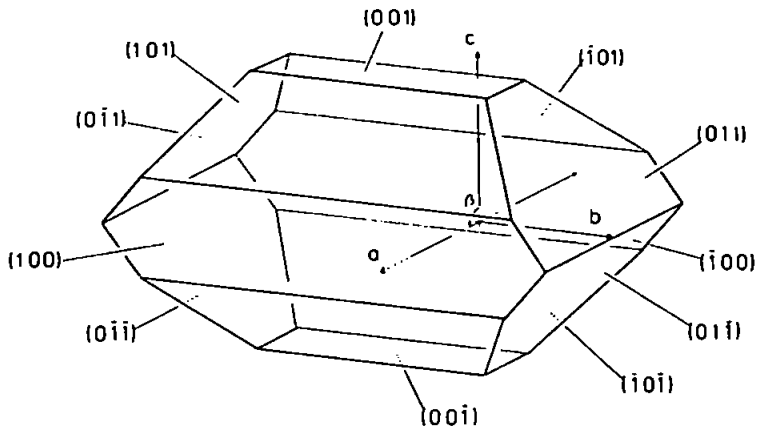
(b) Second crop crystals from same ... ...

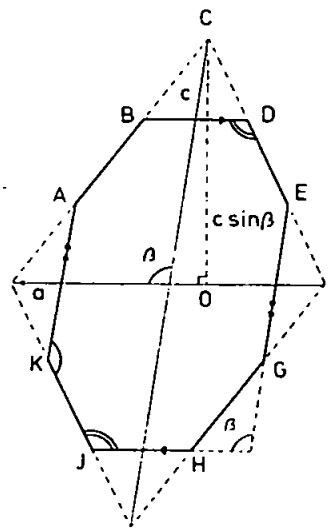


3 a



3 b

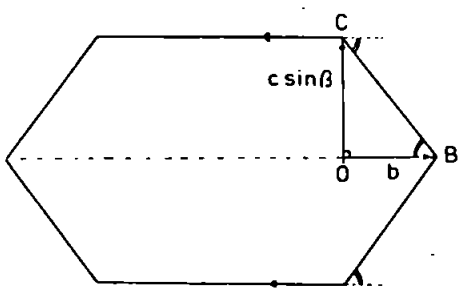




β = 98·6°
(99·0° obs)

∠AKJ = 145·7° calc.
(146·5° ± 5° obs)

∠KJH = ∠BDE
= 115·7° calc
(115·3° ± 5° obs)



∠OBC = tan⁻¹(c sinβ/b)
= 52·45° calc.
(52·2° ± ·5° obs)

Fig 1·3 - CRYSTAL INDICES OF SECO-PENICILLIN

EB - 976.

acetate, and chloroform. Colourless monoclinic crystals were obtained from a range of solvent systems, either by slow cooling or evaporation, the crystal habit varying with solvent as illustrated in Fig 1.2. Crystal faces were indexed from interfacial angle measurements, as shown in Fig 1.3.

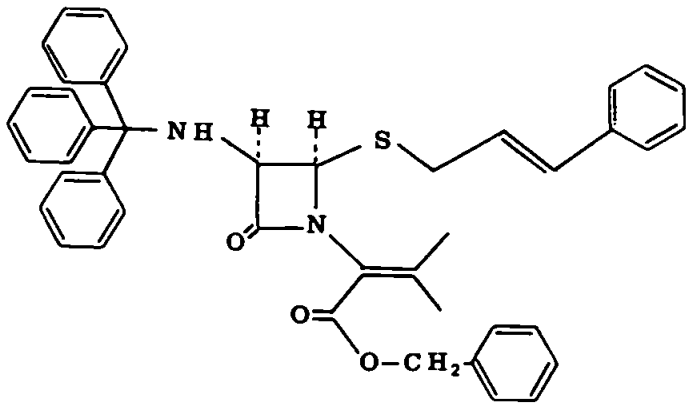
The prisms from acetone - water, and ethylacetate-acetone water, illustrated in Plate 2(a), Fig 1.2(a) and Plate 2(b), Fig 1.2(b) respectively displayed faces of forms $\{100\}$ and $\{110\}$, and were elongated in the direction of the crystallographic b-axis. The crystals from the second of these systems were of slightly better quality than those from the first, but their tabular shape was unsuitable for structure determination.

First crop crystals from chloroform heptane, were also elongated along the b-direction, and displayed additional faces of form $\{101\}$ as illustrated in Fig 1.2c and Plate 3(a), sometimes to the exclusion of faces $(100)(\bar{1}00)$. Second crop crystals were of very different appearance, being elongated along the a and c directions relative to b, and usually showing only the fully developed faces of forms $\{101\}$ and $\{011\}$ as in Fig 1.2d, Plate 3(b).

Crystals grown from the single solvents ethanol, isopropanol, and ethyl acetate were opaque, and of poor quality relative to those described above.

The crystals obtained from acetone-water, were used in the determination of the lattice constants and crystal structure, of the seco penicillin as described in detail in Chapter 4.

(iii) (3R, 4R) - 1 - (1 - benzyloxycarbonyl - 2 - methyl - prop - 1 - enyl) - 4 - (cinnamylthio) - 3 - (triphenylmethylamino) - azetidin - 2 - one. (Ref E.B. 986)



3.

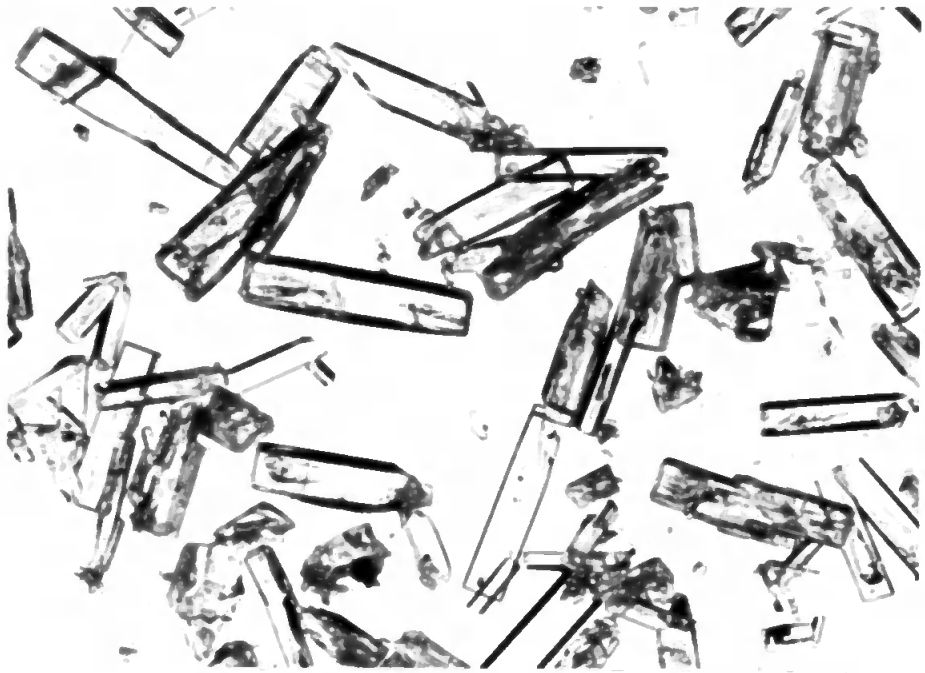
The seco penicillin 3, which differs from 2 only in the substitution of the sulphur atom, was very soluble in ethyl acetate and acetone, sparingly soluble in ethanol, and almost insoluble in petrol or heptane. The best crystals were obtained by slowly cooling a solution of 50 mg of 3 in 0.3 ml ethyl acetate to which had been added 1.4 ml warm ethanol Plate 4(a). Slow evaporation of the mother liquor yielded the large tabular crystals illustrated in Plate 4(b), which show additional small faces. Fairly good crystals were also formed from ethyl acetate petrol/heptane, but the results from acetone-water were very dependent on the amount of water added.

The crystals shown in Plate 4(a), were indexed from unit cell data and interfacial angle measurements as illustrated in Fig 1.4. Preliminary X-ray measurements showed this seco compound to belong to the orthorhombic crystal system, unlike the methylallyl analogue 2, which is monoclinic. The measured density, 1,212 kg/m^3 determined by flotation in chloroform cyclohexane is in agreement with the value 1,213 kg/m^3 calculated for Z = 4 molecules per unit cell. The approximate cell dimensions were found to be, a = 7.7 Å, b = 11.1 Å, c = 41.9 Å.

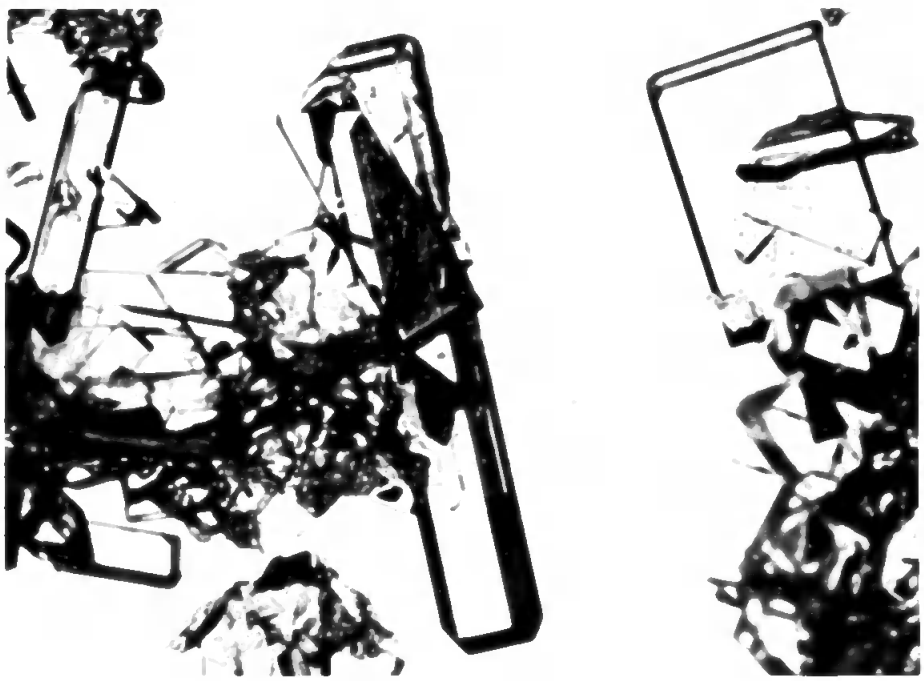
PLATE 4: The cinnamylthio seco penicillin, E.B. 986

(a) Crystals obtained by slow cooling from ethyl acetate-ethanol ... ...

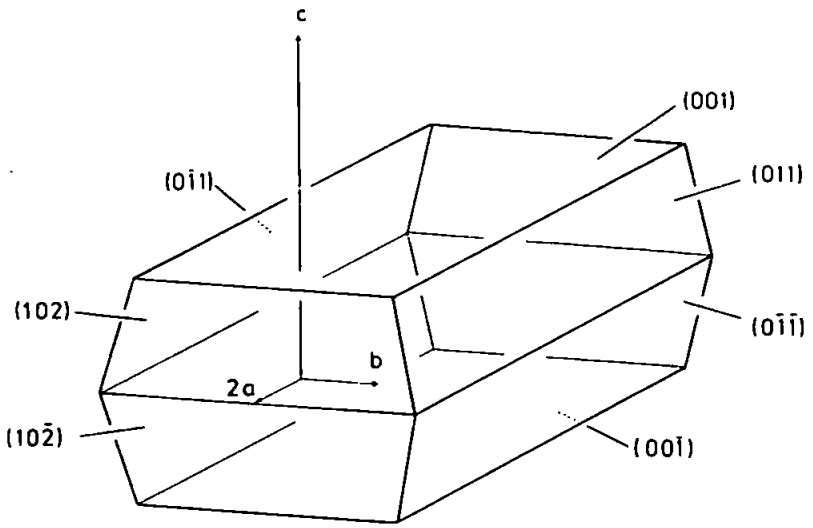
(b) Second crop crystals obtained by slow evaporation of liquor from (a) ... ...

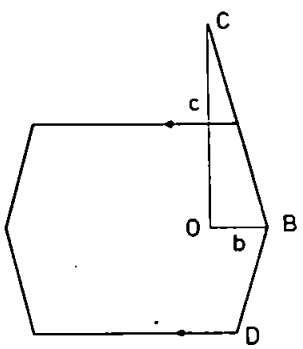


4 a

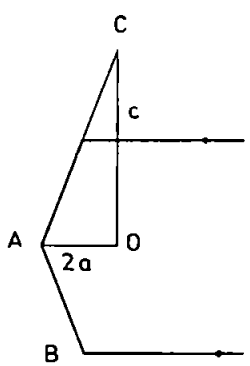


4 b





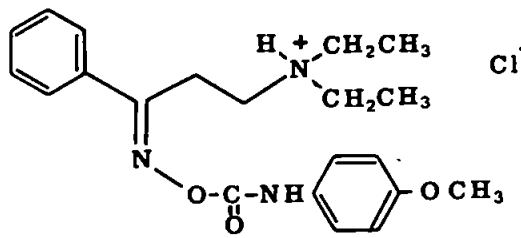
$\angle OBC = 1/2 \angle DBC$
$= \tan^{-1} c/b$
$= 75{\cdot}2^{\circ}$ (Obs. $75{\cdot}2^{\circ} \pm {\cdot}5^{\circ}$)



$\angle OAC = 1/2 \angle BAC$
$= \tan^{-1} c/2a$
$= 69{\cdot}8^{\circ}$ (Obs. $70{\cdot}3^{\circ} \pm 5^{\circ}$)

Fig. 1·4 CRYSTAL INDICES OF CINNAMYLTHIO SECO-PENICILLIN, EB-986.

(vi) 0 - (4 - methoxyphenylcarbamoyl) - 3 - diethylamino-propio-phenone oxime hydrochloride (anidoxime) (Ref BRL 11870)



4.

The hydrochloride, 4, yielded excellent crystals, from a 10% w/v aqueous solution, prepared using deaerated distilled water at 40 - 50°C. The hot solution was filtered and quickly cooled to room temperature in a closed flask, to minimise decomposition. Air was evacuated from above the solution, which was then protected from light and allowed to crystallise over 15 hours. The colourless transparent prisms were isolated and quickly dried between filter paper. Exposure to light caused the crystals to become brown within several hours, while solutions decomposed rapidly in daylight becoming pink in less than an hour. The compound is known to decompose to bis (4 - methoxyphenyl) urea in solution.

Plate 5 shows typical anidoxime crystals, which may reach dimensions 5 x 1 x 1 mm, elongated parallel to the crystallographic a-axis. Crystals usually showed the four faces of form $\{011\}$ and in large specimens, additional smaller faces (010) and (001) were also observed. The appearance of crystals varied with the development of $(10\bar{1})$ relative to (111) and $(1\bar{1}1)$ as illustrated in Fig 1.5.

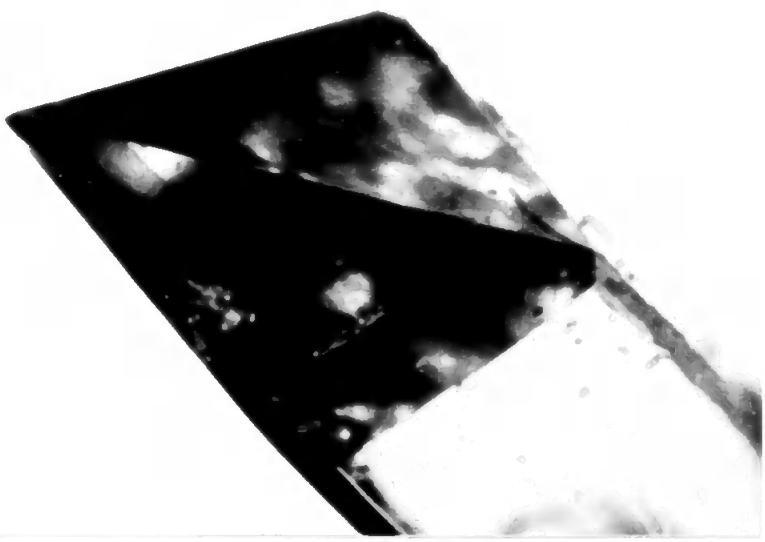
The crystal structure of anidoxime was determined, as described in Chapter 5, using crystals grown by the above procedure.

PLATE 5: Anidoxime crystals

(a) Typical clusters from aqueous solution ... ...

(b) Terminal faces of a large crystal (1 mm x 1 mm x 4 mm) ... ...

5 a



5 b

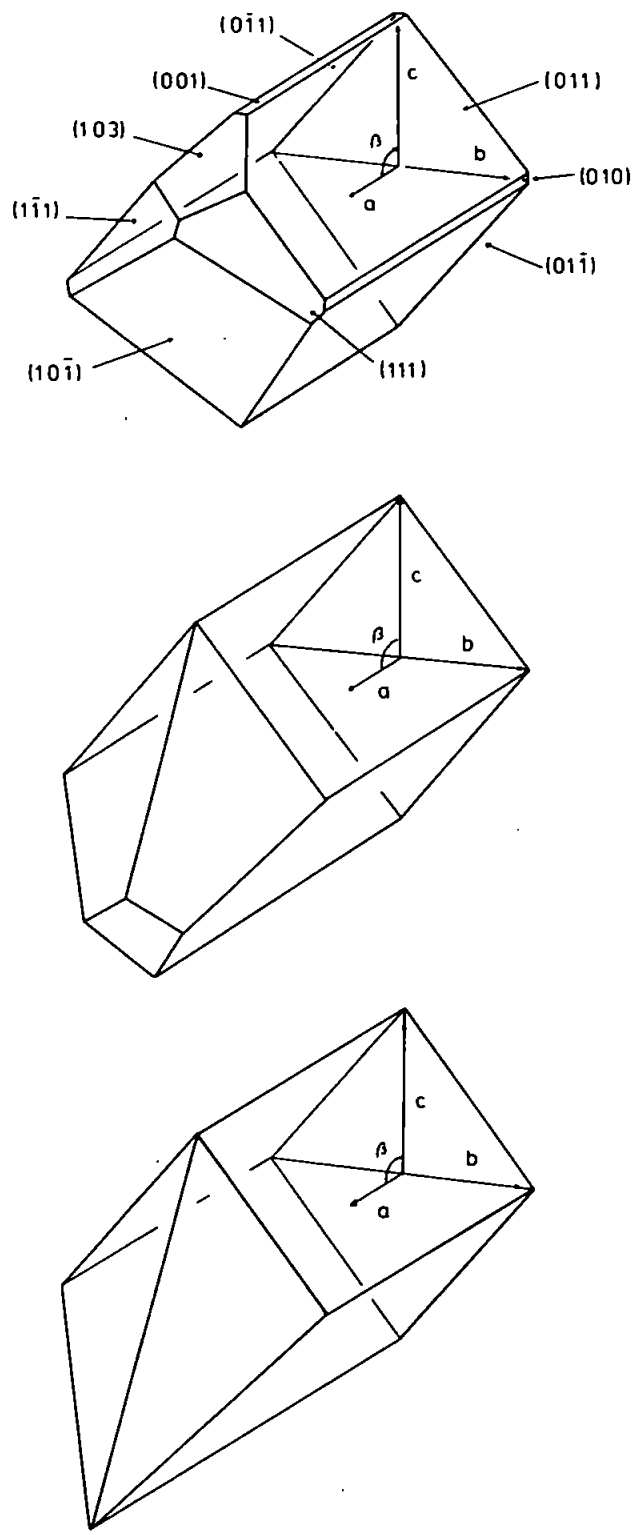
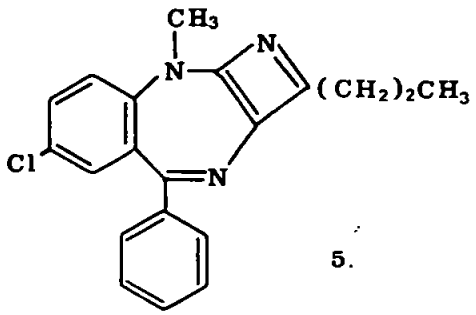


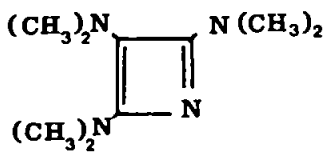
Fig 1·5- CRYSTAL INDICES AND FORM DEVELOPMENT OF ANIDOXIME, BRL.11870.

(v) 8-chloro-1-methyl-4-prop-1-yl-6-phenyl-azeto [2,2b] [1.4] benzodiazepine



5.

The novel pharmacalogically active azete (5) provided by Dr.G. Kirk, Dept. of Pharmacy of Chelsea College, University of London, is of interest because it is derived from the psychoactive drug Librium, and contains the highly strained azete system. Only a few azete compounds have been reported, and the stability of monocyclic azetes, for example (6) Seybold et al, 1973 [1], is very low.



6.

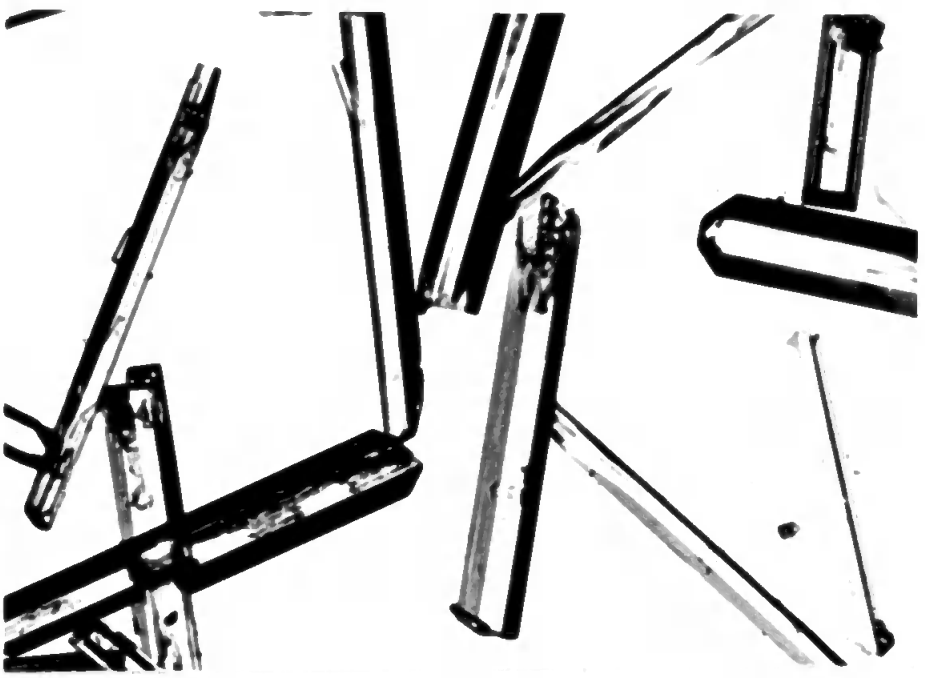
The chemical structure of (5) is supported by physical evidence, C_{13}NMR, H_1NMR, mass spectroscopy data, for example being consistent with the structure shown. Crystals of the azete were required, in order that this evidence could be confirmed by structure determination.

The best crystallisation solvent was found to be acetone, and when a solution of 104 mg of (5) in 5 ml acetone was allowed to cool from 45°C to room temperature over two hours, colourless rod shaped crystals, Plate 6, were obtained, up to 1 cm in length. These were superior in both size and quality to the very fine, small needles obtained from either ethyl acetate or methanol under similar conditions.

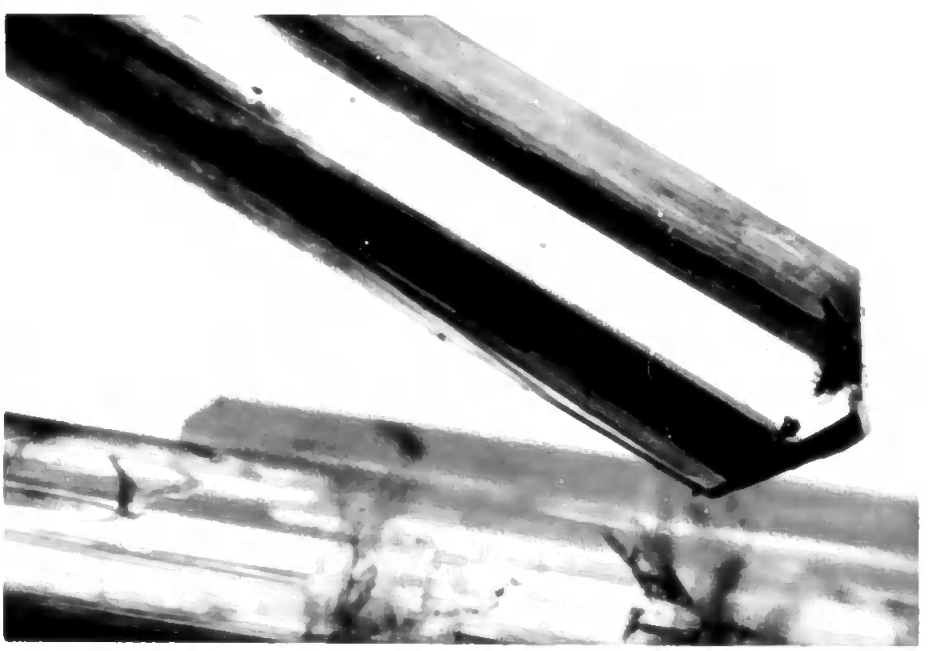
PLATE 6: The azete SH 62

(a) Rods from acetone ... ...

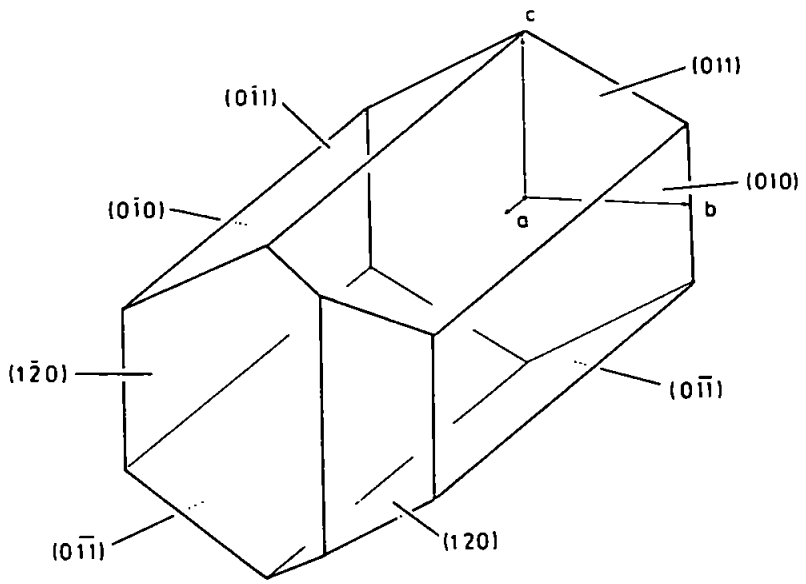
(b) Terminal face detail ... ...

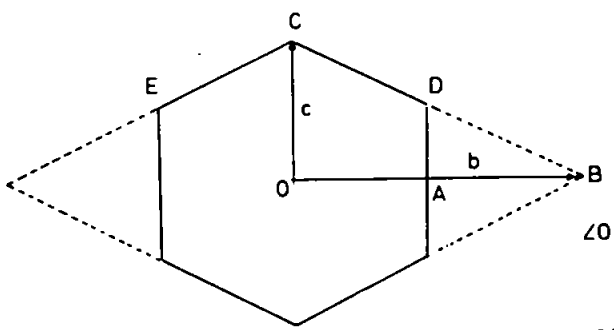


6a

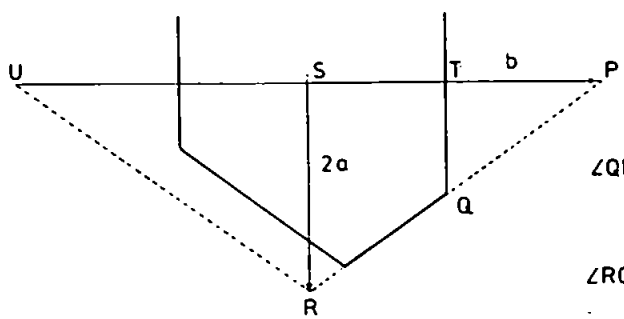


6b





$\angle OCB = 1/2\angle ECB$
$= \tan^{-1} b/c$
$= 63{\cdot}4^\circ$ (Obs. $63{\cdot}5^\circ \pm {\cdot}5^\circ$)
$\angle CDA = 116{\cdot}6^\circ$ (Obs. $116{\cdot}5^\circ \pm {\cdot}5^\circ$)



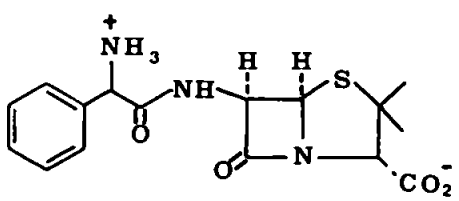
$\angle QRS = 1/2\angle QRU$
$= \tan^{-1} b/2a$
$= 54{\cdot}5^\circ$ (Obs. $55{\cdot}0^\circ \pm {\cdot}5^\circ$)
$\angle RQT = 125^\circ$ (Obs. $125{\cdot}0^\circ \pm {\cdot}5^\circ$)

Fig 1·6 - CRYSTAL INDICES OF AZETE, SH-62.

Preliminary X-ray investigations showed the crystals to belong to the orthorhombic system, and to have unit cell parameters, a = 7.427(17), b = 21.556(11), c = 10.687(8) Å. The crystals were elongated in the direction of the crystallographic a-axis, which was the zone axis for crystal faces of forms {010} - pinacoids, and {011} - domes. Crystals also displayed terminal faces of form {110}, Fig (1.6).

The density was determined by flotation in potassium iodide solution, to be 1,293 kg/m^3. For a structure having Z = 4 molecules/unit cell, the density calculated using relationship 2.3 is 1.303 kg/m^3. Weissenberg photographs of crystals rotated about two orthogonal axes, showed systematic absences 0k0, k = 2n + 1 and h00, h = 2n + 1, indicating that the azete belongs to space group $P2_12_12$.

(vi) Ampicillin anhydrate



7.

Ampicillin, which exists as the Zwitter ion 7, crystallises from aqueous solution as fine colourless prisms of the trihydrate at temperatures below about 40°C. At higher temperatures the trihydrate is thermodynamically unstable with respect to the anhydrate and interconversion occurs, to yield anhydrate as the exclusive product above 60°C, Austin et al, 1965 [2]. The solubility of the anhydrate decreases with temperature, and when excess trihydrate is heated in water, the net result is the gradual dissolution of trihydrate with simultaneous crystallisation of anhydrate to maintain saturation. The anhydrate crystals are generally very small and of poor quality, and conditions were sought which might yield material suitable for single crystal structure determination.

The finely divided trihydrate was found to dissolve more rapidly and the transition was more easily observed in solutions containing 10 - 15% ethanol or isopropanol. Since larger crystals are usually obtained from solutions containing relatively few particulate nuclei, sufficient solvent was used, to completely dissolve the trihydrate at 60 - 70°C. In practice, some anhydrate often crystallised before the last trace of trihydrate had dissolved, but the procedure gave rather larger crystals than were obtained when a large excess of trihydrate was present.

In a typical preparation 30 ml of water at 90°C was added to a suspension of 3.0 g powdered ampicillin trihydrate in 5 ml water and 5 ml isopropanol. The suspension was then heated at 75°C above a hotplate for 2 - 3 minutes by which time most of the solid had dissolved. The flask was then clamped in a water bath the initial temperature of which was 90°C. After two minutes, the solution had become clear and anhydrate crystals had commenced growing with more material appearing as the solution temperature increased from 80°C to 90°C. After a further two minutes the anhydrate was isolated by filtration through a pre-heated Buchner funnel. Recovery was low, being approximately 0.3 g.

Even the best crystals were only marginally acceptable for single crystal X-ray work, and many showed internal cracks. Extension of the heating period at 85 - 95°C beyond four minutes gave no improvement, and lowered the yield, due to decomposition. In a variation of the method 35 ml water and 3 ml isopropanolwere added to 3.0 g trihydrate, and the suspension placed in a water bath initially at 75°C. The bath temperature was increased to 90°C over 13 minutes with occasional agitation. The final temperature of the clear supernatant solution was 89°C. The solution showed less discolouration than was observed in experiments conducted at 95 - 98°C and the yield was greater - 0.95 g.

PLATE 7: Ampicillin anhydrate

(a) Material from water : isopropanol 85:15 ...

(b) Enlargement to show terminal face detail ...

7a

7b

PLATE 8: Ampicillin anhydrate

from water : isopropanol 20:80 ... ...

Ampicillin anhydrate crystals are illustrated in Plate 7, from which it is apparent that there are several form combinations involved in the arrangement of terminal faces. Most frequently, the terminal planes hkl make intercepts on the b- and c- axes in the ratios 6b : 1c or 1b : 1c. The crystals are always elongated along the direction of the b axis, and usually display pinacoids (100) ($\bar{1}$00) and hemidomes (10$\bar{1}$) ($\bar{1}$0$\bar{1}$) parallel to b. Attempts to index the terminal faces were unsuccessful because of the difficulty experienced in obtaining angular measurements.

Crystals prepared by the first of the methods described above, and similar to those in Plate 7, were used for data collection in the determination of the crystal structure of ampicillin anhydrate, Boles and Girven, 1976 [3].

When the conversion was effected by heating 3.0 g trihydrate in 24 ml isopropanol and 6 ml water, at 78°C for 11 minutes, 2.2 g anhydrate was recovered. The crystals were extremely small, the largest being no more than 0.2 mm x 0.04 mm x 0.04 mm but were well formed, and often doubly terminated, as illustrated in Plate 8. The crystals display four faces parallel to the long axis, and terminate in a pair of faces at either end. Indices could not be assigned with any confidence because of the difficulty of obtaining accurate angulon measurements on crystals of this size.

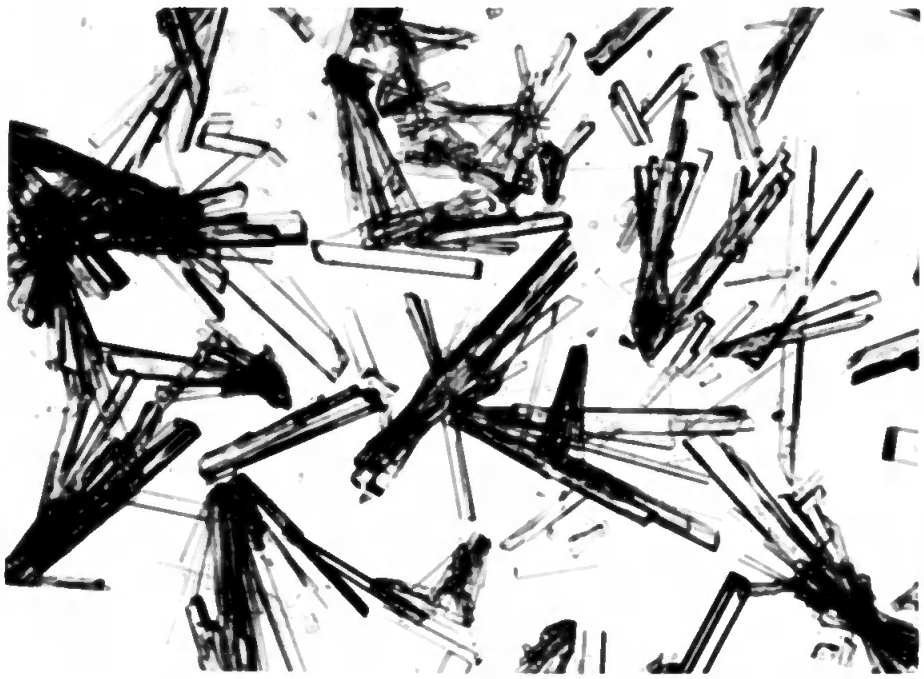
(vii) Ampicillin Trihydrate

The trihydrate was obtained as long transparent needles typically 0.02 x 0.02 x 4 mm by neutralisation of a solution of ampicillin hydrochloride, 0.1 - 0.5 N with equivalent sodium hydroxide. The rate of crystallisation may be influenced by concentration, or the presence of added water miscible solvents, such as ethanol, and somewhat larger crystals were obtained when ethanol or isopropanol were present.

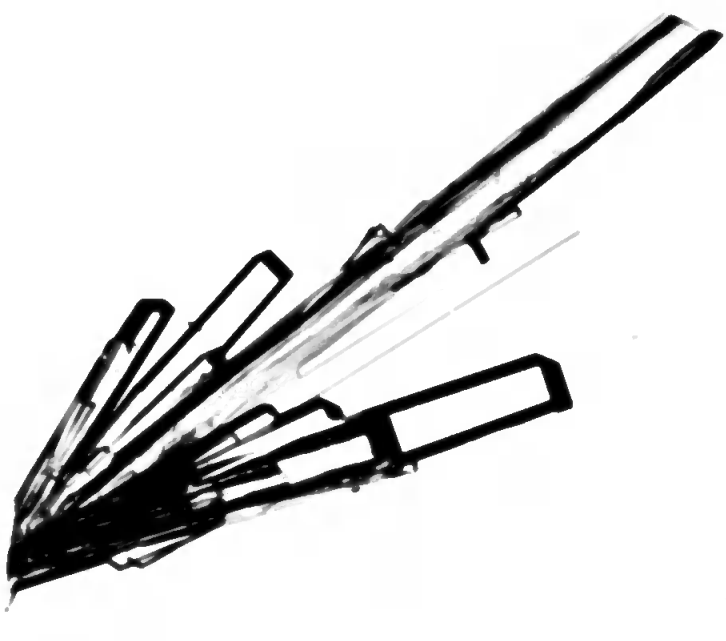
PLATE 9: Ampicillin trihydrate

(a) Clusters of crystals ... ...

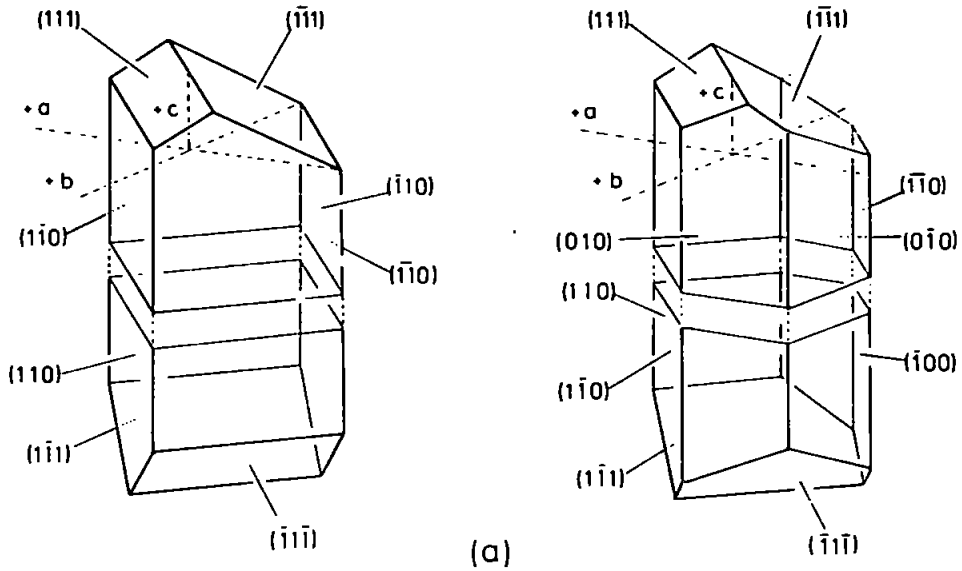
(b) Enlargement to show detail ... ...



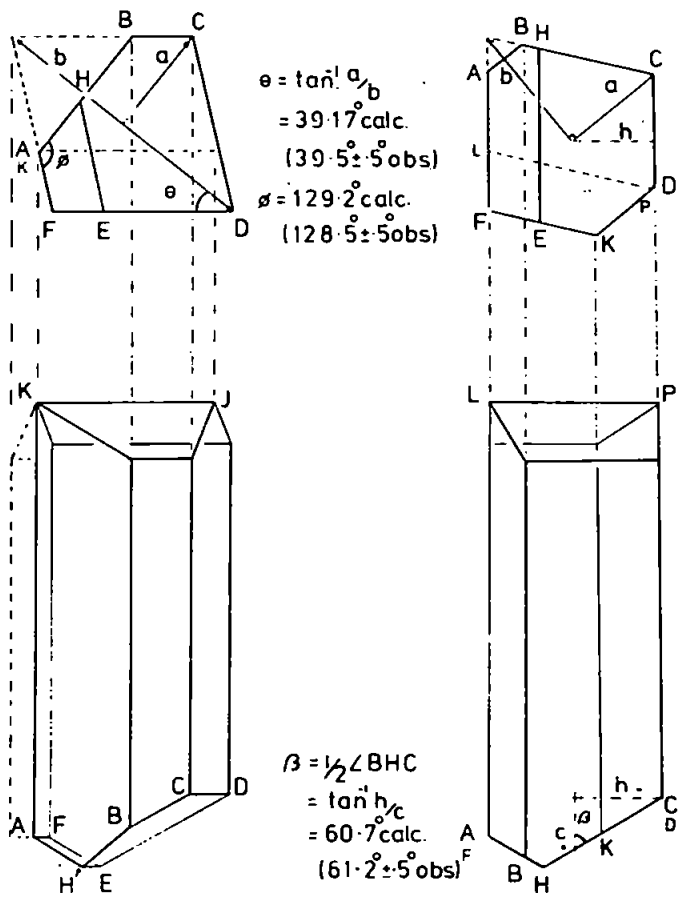
9 a



9 b



(a)



(b)

Fig. 1·7 – CRYSTAL INDICES OF AMPICILLIN TRIHYDRATE

The orthorhombic prisms of trihydrate are elongated along the crystallographic c-axis, and small crystals usually show prism faces $\{110\}$ with pairs of terminal faces (111), $(\bar{1}\bar{1}1)$ at one end and $(\bar{1}1\bar{1})$, $(1\bar{1}\bar{1})$ relative to the same axial directions, at the other, as shown in Fig 1.7a(i). Larger crystals frequently display one or more additional pinacoid faces, predominantly of form $\{010\}$, as in Fig 1.7a(ii). Faces of form $\{001\}$ were not observed on any of those examined. The appearance of crystals viewed normal to the c-axis is illustrated in Fig 1.7(b) for crystals in two orientations. The (111) and $(\bar{1}\bar{1}1)$ faces at the ends of crystals are almost invariably of unequal size and some crystals show only one face at either, or both ends. Typical trihydrate crystals are illustrated in Plate 9.

CHAPTER 2

SINGLE CRYSTAL X-RAY TECHNIQUES

2.1 Introduction

Diffraction of X-rays by a regular crystal lattice, first demonstrated by Von Laue in 1912 has been developed to the extent that the methods of single crystal X-ray structure determination are conveniently applied to complex organic structures. The phase problem remains the main obstacle to routine structure determination and the methods used to solve a given structure depend on the type of structure, for example whether or not it contains a heavy atom, and to some extent on the personal choice of the investigator.

This chapter describes briefly the major experimental and analytical methods which are relevant to the structural investigations described in later chapters. Some of the methods are common to all of the structures, for example all of the intensity data has been compiled from equi-inclination Weissenberg films, while others are appropriate to certain of the structural investigations only.

Extensive use has been made of standard texts in the field of X-ray Crystallography, particularly the works of M. J. Buerger,[4] M. M. Woolfson,[5] E. W. Nuffield,[6] G. H. Stout and L. H. Jensen,[7] and International Tables for X-ray Crystallography.[8]

2.2 The Weissenberg Method and its Applications

A Phillips PW 10/10 X-ray generator operating at 34 KV, 20 mA with a Cu tube and Ni filter was used throughout. (λ = 1.5418 Å) All of the X-ray measurements were made on films obtained from either the Stoe or Nonius Weissenberg cameras. The information obtained from these measurements was used for:

A. Determination of cell dimensions.
B. Space group information.
C. X-ray intensity measurements.

The zero layer Weissenberg measurements were obtained by the normal beam method and the upper layers by the equi-inclination method. The techniques used are well known and described fully in Refs. 3 and 4 and only the derivation of the major results will be described.

2.3 Determination of Cell Dimensions

An approximate value of the repeat distance along the rotation axis was obtained from oscillation photographs using the relationship -

$$r = \frac{\lambda}{\zeta_1} = \frac{n\lambda}{\text{Sin}\left\{\tan^{-1}\left[\frac{Yn}{R}\right]\right\}} \quad \ldots\ldots \text{Eqn. 2.1}$$

where:

ζ_1 = perpendicular distance between adjacent reciprocal lattice levels.

ζ_n = perpendicular distance between zero and nth reciprocal lattice levels.

Yn = distance on film from zero to nth layer lines.

R = true film radius.

The reciprocal lattice constants of the two remaining axes were obtained from zero layer Weissenberg photographs, by measuring the perpendicular distance 2 Yn between equivalent axial reflections on opposite sides of the film. Then,

$$\xi n = 2 \text{ Sin } Yn \quad \ldots\ldots \text{Eqn. 2.2}$$

where ξn = distance from origin to nth reciprocal point. Relationships 2.1 and 2.2 assume the standard camera diameter of 57.3 mm, and Yn measured in mm. The unit cell angles were determined from the separation of the axial lines on zero level Weissenberg photographs. For accurate determination of cell parameters, zero level Weissenberg photographs calibrated with annealed gold wire were taken about two axial directions. Distances between the α_1, components of a number of pairs of equivalent high angle reflections on either side of the film were measured with an illuminated graticule. Ten or more reflections were measured and the 2θ

values derived in this way were refined by means of the PARAM programme of the X-ray 74 System.

2.4 Space Group Determination

While the crystal system may be deduced from the symmetry displayed in oscillation and Weissenberg photographs, and the interaxial angles observed in the latter, space group determination requires knowledge of the number of molecules in the unit cell and identification of the symmetry elements by which they are inter-related. The number of molecules per unit cell, Z, is determined from the known molecular weight, the unit cell volume, and the measured density, by means of the relationship -

$$Z = \frac{V \rho N_o}{M} \qquad \text{..... Eqn. 2.3}$$

where -

No = Avogadro's number 6.023×10^{23} molecules/gm molecular weight.

V = Volume of unit cell, in cm^3.

M = Molecular weight, in gm.

ρ = Measured density, gm cm^{-3}.

Translational symmetry elements in the crystal lattice cause systematic extinction of certain classes of reflections by destructive interference, and the pattern of absences in Weissenberg photographs provides space group information. Symmetry elements frequently encountered in organic crystals include 2-fold screw axes (2_1) and glide planes.

The result of a 2_1 axis is to effectively halve the spacing of planes normal to the axis, thereby causing phase cancellation of all odd-order reflections from these planes. The interleaving of planes caused by the screw axis bears no simple relationship to the spacing of other planes and the only reflections extinguished are those of type, h00 for h = 2n + 1, 0k0 for k = 2n + 1 and 00l for l = 2n + 1.

The appearance of the pattern of absences resulting from the interleaving effect of glide planes depends upon the rotation axis chosen,

and upper level photographs are necessary to distinguish between axial absences caused by a 2_1 axis, and those which result from rotation about an axis which is in the glide plane but normal to the translation component of the glide. (ref. 7 - CH 5).

The extinctions patterns produced by complex space groups result from superposition of those derived from individual symmetry elements. For example, in space group $P2_1/c$, for rotation about the a - axis, the absences result from the effects of the 2_1 axis along b, which extinguishes only reflections of class 0k0 for k = 2n + 1, and the glide plane normal to b. which extinguishes reflections h0l where l = 2n + 1.

Most space groups are not uniquely defined by systematic absences, which provide no information regarding the presence or otherwise of a centre of symmetry. A centre of symmetry may sometimes be inferred or confirmed from the statistics of intensity distribution, as described in ref. 7 - CH 7. The intensities of reflections from noncentrosymmetric crystals tend to be more tightly bunched about their mean than are those from centrosymmetrical crystals. A plot of N(Z) the fraction of reflections of intensity less than a certain fraction Z, of the average intensity, vs.Z, yields a curve which will resemble one or other of the theoretical curves for centric or acentric distributions. Fig 2.1

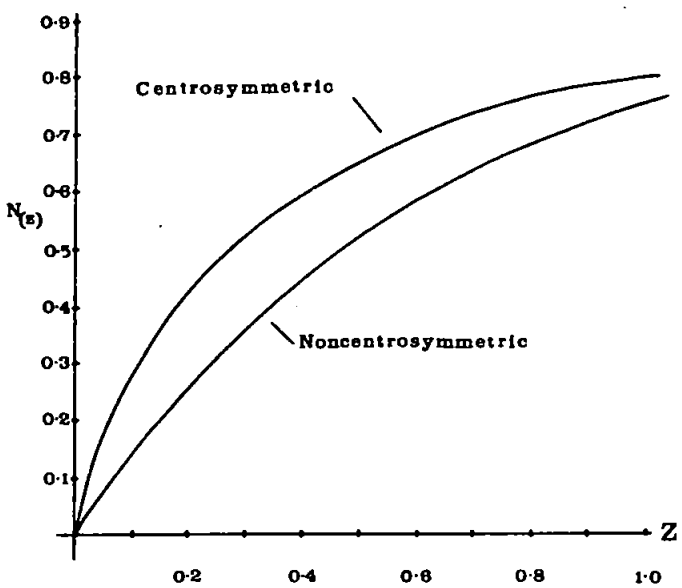


Fig 2·1 Intensity distribution curves

Statistical analysis of intensity distributions is routinely incorporated in data reduction programmes to enable comparison of observed vs theoretical distributions.

2.5 X-Ray Intensity Measurements

The X-ray reflections for intensity measurement were obtained by the multiple film technique, using Ilford Industrial G X-ray film. For most layers a pack of 5 films was used for a long exposure (typically 100 hrs) and when necessary a short exposure was obtained in order to render the intense reflections within the measurable range of the films. The film factor was determined between film pairs from the ratio of intensities of a number of reflections of measurable intensity on both films.

In the very early stages of the work, the intensities were measured by visual comparison with a precalibrated scale, made from varying exposure times of one reflection from the crystal. This method was abandoned when the Science Research Council Microdensitometer Service became available, using the Optronics International System P-1000 Photoscan. The intensity measurements from a given data set were approximately on the same scale, as the times of the long exposures were constant and data from the short exposures was scaled to this.

2.6 The Interpretation of Intensity Data

The measured intensities from all crystal planes hkl are related to the atomic content and the structure within the unit cell. In addition the measured intensities are subject to geometrical and physical factors for which corrections must be made. The correction factors and the initial calculations involved in the data reduction are now described:

a. Lorentz - Polarisation Factor Lp.

The Lorentz factor L is a correction applied to measured intensities

in order to account for the difference in time that the reciprocal lattice points take to pass through the surface of the reflecting sphere. It is related to the Bragg angle 2θ and the equi-inclination angle μ by -

$$L = \frac{\sin\theta}{\sin 2\theta\sqrt{\sin^2\theta - \sin^2\mu}} \quad \text{..... Eqn. 2.4}$$

Polarization of the reflected beam increases with 2θ and causes a reduction of reflected intensity. The correction takes the form -

$$p = 1 + \frac{\cos^2 2\theta}{2} \quad \text{..... Eqn. 2.5}$$

and is applied to the measured intensities in conjunction with the Lorentz factor.

$$Lp = \frac{\sin\theta}{\sin 2\theta\sqrt{\sin^2\theta - \sin^2\mu}} \cdot \frac{1 + \cos^2 2\theta}{2} \quad \text{..... Eqn. 2.6}$$

and $$I_{hkl}(\text{relative}) = \frac{I_{hkl}\ (\text{measured})}{Lp}$$

The structure amplitude, $|F_{hkl}| = \sqrt{KI_{hkl}\ (\text{relative})}$ ..... Eqn. 2.7

where K is the scale factor required to place the relative intensities on an absolute basis.

b. Scattering factor f.

Atoms occupy a finite volume and the apparent intensity of reflected X-rays is reduced by the phase difference between rays scattered from different regions of the atom. The ratio of the amplitude scattered by an atom to that scattered by an electron is defined as the scattering factor f. At $\theta = 0^\circ$, f = Z, while at higher angles the effect is a reduction in the measured intensity. Scattering factors used in this work were taken from International Tables for X-Ray Crystallography, Vol 3, or Acta. Cryst., A24 (1968) 321.

c. The Temperature Factor

Thermal motion increases the effective atomic volume, thereby causing a more rapid decrease of scattering power with increasing θ in real atoms, than would be observed for atoms at rest. For isotropic vibrations the corrected scattering factor is -

$$f = f_o e^{(-B \sin^2\theta/\lambda^2)} \quad \text{..... Eqn. 2.8}$$

where f_o = scattering factor for an atom at rest

and $B = 8\pi^2 \overline{u}^2$

$\overline{u}^2$ is the mean square amplitude of vibration, in $\mathring{A}^2$ units, and the exponential term is known as the Debye-Waller factor. For the general anisotropic case, the temperature factor is -

$$e^{-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)} \quad \text{..... Eqn. 2.9}$$

where U_{ij} are the thermal parameters expressed in terms of mean square amplitudes of vibration in $\mathring{A}$.

The isotropic temperature factor has been used in structure determination up to the final stages of refinement. An initial overall isotropic temperature factor was determined from the Wilson plot, described in the next section, and anisotropic thermal motion was detected from difference Fourier synthesis, as described in section 2.15.

2.7 The Wilson Plot

An estimate of the average value of B for a structure, and the overall scale factor relating I (absolute) to I (relative) may be obtained from a Wilson plot; Wilson 1942.[9] The quantity $\ln\left\{\frac{\bar{I}_{rel}}{\sum_{j=1}^{N} fo_j^2}\right\}$ is calculated for all reflections within given ranges of $\sin^2\theta/\lambda^2$, within which f is assumed constant, and plotted against $\sin^2\theta/\lambda^2$. Fig 2.2

The slope of the straight line obtained is -2B. The intercept at $\sin^2\theta/\lambda^2 = 0$ is ln C, from which may be obtained K the scale constant relating $|Fabs|$ to $|F_{rel}|$.

$$K = \frac{1}{\sqrt{C}}$$

$$|Fabs| = K\,|F_{rel}|$$

$$\therefore \quad |Fabs| = \frac{1}{\sqrt{C}} \cdot |F_{rel}| \qquad \text{..... Eqn. 2.10}$$

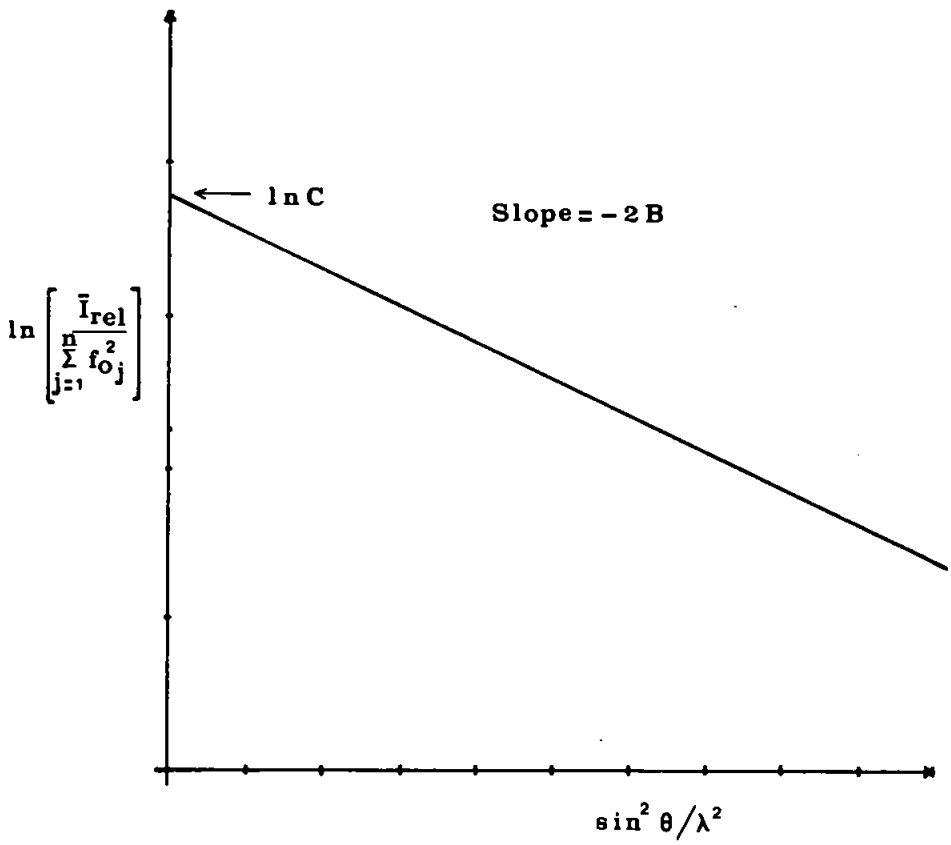


Fig 2.2 The Wilson Plot

2.8 The Structure Factor

The structure factor F_{hkl}, illustrated in Fig 2.3 is the vector sum of the j waves scattered in the direction hkl by the j atoms in the unit cell,

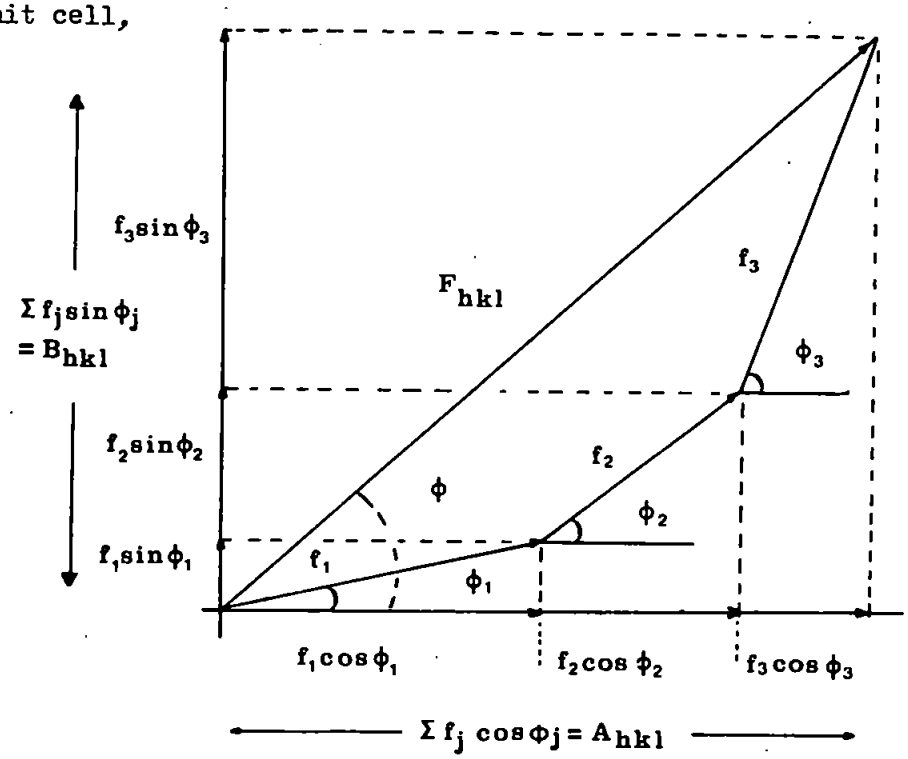


Fig 2.3 The structure factor, F_{hkl}

- where $\phi_j = 2\pi(hx_j + ky_j + lz_j)$.

In complex notation.

$$F_{hkl} = \Sigma\left[f_j \cos\Phi_j\right] + i\,\Sigma\left[f_j \sin\Phi_j\right] \qquad \text{.....Eqn. 2.11}$$

which by use of the identity $e^{i\Phi} = \cos\Phi + i\sin\Phi$

may be expressed in exponential form as -

$$\left|F_{hkl}\right| = \sum_j f_j\, e^{\left[2\pi i\,(hx_j + ky_j + lz_j)\right]} \qquad \text{.....Eqn. 2.12}$$

From Fig (1)

$$F_{hkl} = \sqrt{A_{hkl}^2 + B_{hkl}^2} \qquad \text{.....Eqn. 2.13}$$

where

$$A_{hkl} = \sum_j f_j \cos 2\pi\,(hx_j + ky_j + lz_j)$$

$$B_{hkl} = \sum_j f_j \sin 2\pi\,(hx_j + ky_j + lz_j)$$

The phase of F_{hkl} is given by,

$$\phi_{hkl} = \tan^{-1}\left\{ \frac{B_{hkl}}{A_{hkl}} \right\} \qquad \text{..... Eqn. 2.14}$$

2.9 The Structure Factor in terms of Electron Density

The structure factor may be regarded as the resultant of wavelets scattered from all the infinitesimal elements of electron density in the unit cell, and without any assumptions regarding the distribution of electron density, an expression may be derived, relating the structure factor to electron density. If the electron density ρ is defined as electrons per unit volume, the number of electrons in a volume element dv at xyz is given by $\rho_{(xyz)}dv$. The wavelet scattered from this element, in exponential form is given by -

$$\rho_{(xyz)} e^{2\pi i (hx + ky + lz)} \qquad \text{..... Eqn. 2.15}$$

The structure factor, which is the sum of all the wavelets scattered from the unit cell, may therefore be expressed as -

$$F_{hkl} = \int_0^V \rho_{(xyz)} e^{2\pi i (hx + ky + lz)} dv \qquad \text{.....}^{T} \text{ Eqn. 2.16}$$

The spatially periodic distribution of electron density within the crystal may be represented by a three dimensional Fourier series -

$$\rho_{xyz} = \frac{1}{V} \sum_h \sum_k \sum_l F_{hkl} e^{-2\pi i (hx + ky + lz)} \qquad \text{.....}\ T^{-1} \text{ Eqn. 2.17}$$

This expression describes the electron density in direct space in terms of the structure factors in reciprocal space and represents a transform T^{-1} which is the inverse of T whereby the structure factor is described in terms of electron density. The series for ρ_{xyz} may also be expressed more conveniently as,

$$\rho_{xyz} = \frac{1}{V} \sum_h \sum_k \sum_l \left|F_{hkl}\right| \cos 2\pi (hx + ky + lz - \phi^1_{hkl}) \qquad \text{..... Eqn. 2.18}$$

where $\phi^1_{hkl} = \phi_{hkl}/2\pi$, and Friedel's Law is assumed to hold. (ref 7.CH.8)

2.10 The Phase Problem

The solution of a structure requires a knowledge of the structure factor amplitudes and phases of the X-ray reflections in order to calculate the electron density distribution within the unit cell. The measured intensities provide the amplitudes $|F_{hkl}|$, but the phases, which in the general non centrosymmetrical case can have a value between o and 2π, and in the centrosymmetric case are restricted to either o or π, cannot be measured directly.

A number of methods have been successfully used to determine the phases of the reflections. Two major methods have been used in this work.

a. The Patterson or Heavy Atom method, applicable when a small proportion of the atoms in the structure have significantly higher electron content than the remaining atoms.

b. Direct methods, whereby mathematical relationships are determined which inter-relate the phases of reflections, and the phases of a large number of reflections may be determined from a small number of starting phases.

Those methods with particular reference to this work are now described in detail.

2.11 The Patterson Function

Patterson, 1934 [10] 1935 [11], showed that the 3-dimensional function

$$P_{uvw} = \frac{1}{V} \sum_{h=-\infty}^{+\infty} \sum_{k=-\infty}^{+\infty} \sum_{l=-\infty}^{+\infty} |F_{hkl}|^2 \, e^{2\pi i (hu + kv + lw)} \quad \text{..... Eqn. 2.19}$$

represents the average value of the vector product, $P_{(xyz)} \cdot P_{(x+u,\, y+v,\, z+w)}$ over the complete unit cell. Thus for atoms at $x_1\ y_1\ z_1$ and $x_2\ y_2\ z_2$ with atomic numbers z_1, z_2 respectively there corresponds a Patterson vector at uvw where $u = x_2 - x_1$, $v = y_2 - y_1$, $w = z_2 - z_1$,

of peak height proportional to $Z_1.Z_2$. These vectors all radiate from the common origin at which is located a large peak derived from the coincident null vectors.

$$P_{(ooo)} = \frac{1}{V} \sum_{hkl=-\infty}^{+\infty} |F_{hkl}|^2 \times 1 \qquad \text{..... Eqn. 2.20}$$

The n atoms in the unit cell give rise to n (n-1) non-origin peaks, which are subject to considerable superposition since they are contained in a unit cell of the same volume as the n electron density peaks. The overlap is accentuated by the intrinsic broadness of Patterson peaks, which is a consequence of finite atomic volumes. Improved resolution may be achieved if the scattering power is assumed to be concentrated at a point, and therefore independent of $\sin\theta/\lambda$. For a cell containing N identical atoms,

$$F = f \sum_{j=1}^{N} e^{2\pi i (hx_j + ky_j + lz_j)} \qquad \text{..... Eqn. 2.21}$$

For real atoms, $f = f_o e^{-B \sin^2\theta/\lambda^2}$

For point atoms $f = Z$

$$\frac{Fpoint}{Freal} = \frac{Z \sum_{j=1}^{N} e^{2\pi i (hx_j + ky_j + lz_j)}}{f_o e^{-B \sin^2\theta/\lambda^2} \sum_{j=1}^{N} e^{2\pi i (hz_j + ky_j + lz_j)}}$$

$$\therefore \quad Fpoint = \frac{Z}{f_o e^{-B \sin^2\theta/\lambda^2}} \cdot Freal \qquad \text{..... Eqn. 2.22}$$

Most structures contain more than one atomic species, and an average value of Z/f is required. The expression for Fpoint then becomes,

$$Fpoint = \frac{\sum_{j=1}^{N} Z_j \cdot Freal}{e^{-B \sin^2\theta/\lambda^2} \cdot \sum_{j=1}^{N} fo_j} \qquad \text{..... Eqn. 2.23}$$

The sharpened Patterson function uses $Fpoint^2$ as coefficients.

The Patterson function is calculated in 3-dimensional vector space and the values usually printed in sections through the unit cell, which may be contoured at certain values of the function and displayed to yield a 3-dimensional Patterson map. The sharpened Patterson has better resolution than a normal Patterson. By subtraction of the quantity $\sum_{j=1}^{N} Z_j^2$ from each $|\text{Fpoint}|^2$ the origin peak may be removed during the sharpening process.

In general the Patterson method is applied to the determination of heavy atom coordinates in the unit cell, since the peak intensity is proportional to the product $Z_1 \cdot Z_2$ and the Patterson vectors relevant to a small number of heavy atoms can often be easily identified. This method was used to determine one of the present structures and the essential symmetry properties of the Patterson function related to this determination are described in the next section.

2.12 Patterson Symmetry and Space Group Dependent Vectors

Pairs of atoms A and B give rise to two vectors $\vec{AB}$ and $\vec{BA}$ of equal magnitude but opposite direction, the peaks lying at (u, v, w), (-u, -v, -w) and the Patterson map is therefore always centrosymmetric. The lattice type (P,I., etc.) is the same as that of the original space group, and the Patterson space group is derived from the original by replacement of screw axes and glide planes, by rotation axes and mirror planes respectively, and insertion of a centre of symmetry if one is not already present.

Certain sections and lines through the full three dimensional Patterson function contain peaks due to pairs of symmetry related atoms, Harker, 1936 [12]. For example, in space group $P2_1$, pairs of atoms at x, y, z, and $\bar{x}$, $\frac{1}{2}$ + y, $\bar{z}$ give rise to vectors uvw where u = 2x, v = $\frac{1}{2}$, w = 2z, the peaks for which lie in the Harker plane v = $\frac{1}{2}$.

The symmetry related Patterson peaks are particularly useful for the location of a small number of heavy atoms in the structure. The remaining atoms are then located by calculation of an electron density map using the $|F_{hkl}|$ from measured intensities and the phase contribution of the heavy atoms.

In space group $P2_1$, when only a single heavy atom is present in the structure the electron density map calculated from the phase contribution of this heavy atom contains artificial mirror symmetry across the y plane containing the heavy atom and it is necessary to remove this symmetry by the careful introduction into the phasing process, of those atoms which may be uniquely determined. This is given further consideration in the structure determination in Chapter 3.

2.13 Direct Methods

For structures which contain no 'heavy' atoms, the Patterson function is difficult and sometimes impossible to interpret. Direct methods have been developed to the extent that they are commonly used in the solution of complex organic structures. In centrosymmetric structures the relationship between phases of reflections with high F_H (H refers to a reflection with given hkl) is expressed by the Sayre equation, - Sayre 1952 [13], $S_H \sim S_{H'} \cdot S_{H-H'}$ ..... Eqn. 2.24

where S means 'sign of'.

Phase determination by direct methods requires the use of normalized structure factors, E_H defined by -

$$E_H^2 = \frac{U_H^2}{\epsilon \sum_{j=1}^{N} n_j^2} \quad \text{where} \quad U_H = \frac{|F_H|}{e^{-B\sin^2\theta/\lambda^2}.\left(\sum_{j=1}^{N} fo_j\right)}$$

and $-1 \leq U \leq 1$

$$= \frac{|F_H|^2}{\epsilon \sum_{j=1}^{N} f_j^2} \qquad \text{..... Eqn. 2.25}$$

Normalized structure factors do not contain the effects of atomic scattering or thermal motion, and allow normalization of all classes of reflections to a common basis. The term ε, a multiplicity factor is included to reduce the significance of classes of reflections having abnormally high U values due to reinforcement by space group symmetry. The Sayre equation in terms of E's implies that any two reflections with indices H - H' and H', which can be added together to give the indices of a third reflection with indices H, provide one indication of the phase ϕH of H equal to the sum of $\phi H-H'$ and $\phi H'$. The weight of the indication is the product $|E_{H'}| \cdot |E_{H-H'}|$ and the best estimate of ϕ_H is the weighted sum of all indications.

In centrosymmetric structures phases are either o or π, and the addition of phases is represented as the product of signs. The sign indications are summed to yield the sign of the reflection -

$$SE_H = S\left[\sum_{H'} E_{H'} \cdot E_{H-H'}\right] \qquad \text{..... Eqn. 2.26}$$

For non centrosymmetric structures the phases have general values in the range o to 2π. Phase determination by the summation of angles formula $\phi_H \approx \phi_{H'} + \phi_{H-H'}$, while being true for reflections with the highest E_H's, will in general be very approximate.

Phases for non centrosymmetric structures may be conveniently derived by the weighted tangent formula, Germain et al, 1971 [14], illustrated graphically in Fig 2.4.

$$\tan \phi_H = \frac{\sum_{H'} W_{H'} |E_{H'} \cdot E_{H-H'}| \sin(\phi_{H'} + \phi_{H-H'})}{\sum_{H'} W_{H'} |E_{H'} \cdot E_{H-H'}| \cos(\phi_{H'} + \phi_{H-H'})} \qquad \text{..... Eqn. 2.27}$$

$$= \frac{T_H}{B_H}$$

where,

$$W_{H'} = 0.5 + 0.5 \tanh\left[0.5\, Ec_{(H)} \cdot Ec_{(H')} \cdot Ec_{(H-H')}\, \sigma_3 \cdot \sigma_2^{-3/2}\right]$$

where $Ec(H) = (T_H^2 + B_H^2)^{\frac{1}{2}}$

and $\sigma_r = \sum_{j=1}^{N} Z_j$

Z_j is the atomic number of the jth atom, and N is the total number of atoms per unit cell.

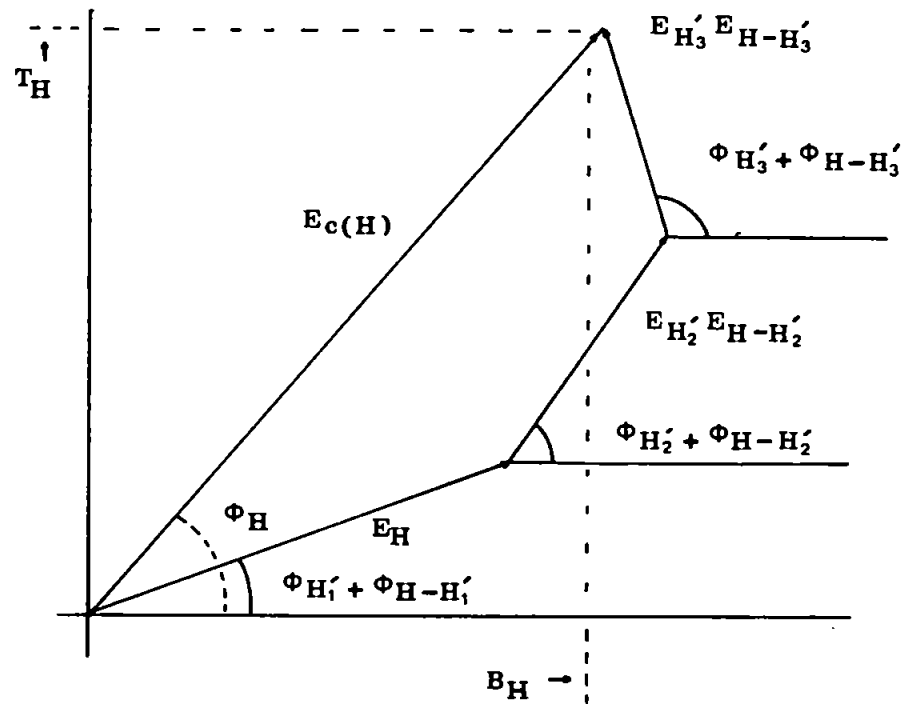


Fig 2·4 The tangent formula

2.14 Application of Direct Methods

The Sayre equation and the tangent formula predict relationships between phases of certain reflections. Application of these methods necessitates prior knowledge of a few phases (the starting set) in order to predict new phases. A convenient and essential knowledge of the phases of 3 reflections is obtained by fixing the phases of these reflections in order to locate the origin of the unit cell on each of its three axes. The reflections must be carefully chosen as the mathematical relationship between the indices varies with space group,

and the phases of these reflections must conform to the restrictions imposed by the space group. A comprehensive treatment of origin determining procedures is given by J. Karle in section 6 of vol. 4 of International Tables for X-Ray Crystallography. The origin determining methods used in this work are discussed in the appropriate chapters.

In non-centrosymmetric space groups the phase of a further reflection must be fixed in order to define the enantiomorph. The enantiomer of a structure can be obtained by reversing the directions of the three axes and this has the effect of changing the phases of all reflections from $+\phi$ to $-\phi$ The enantiomorph determining reflection must be chosen such that its value is not 0° or 180° (since these are not affected by change of $+\phi$ to $-\phi$) and such that its phase is not affected by the translation required to reverse the phase of the origin determining reflections. The phase of the enantiomorph reflection is then chosen to lie within the range 0° to 180° or 180° to 360°. In some space groups this reflection can often be selected so that it is restricted by space group symmetry to have a value of $\pm 90^{\circ}$ and in that case one of these values may be arbitrarily chosen. If this is not so then the reflection may be alternatively given the phase 45° or 135° so that its maximum error is $\pm 45^{\circ}$. The origin and enantiomorph fixing reflections must conform to the rules referred to and also must have high E values, and enter into many interactions with other reflections. The high E values ensure that the phase angles so predicted will have a high probability of being correct.

The above starting set may be sufficient to determine, using the weighted tangent formula, the phases of a large number of reflections of high E. If this is not the case then a limited number of reflections with high E's and many interactions may be given symbols to represent

their phases (the symbolic addition method Karle and Karle 1964 [15], 1966 [16]) or these reflections may be allotted alternative phases and the tangent formula applied to each alternative starting set, to yield a number of solutions, by the multisolution method (MULTAN [14], SHEL-X [17]) particular methods used in this work are described in the appropriate chapters.

2.15 Fourier Refinement

Interpretation of the Patterson heavy atom method provides the coordinates of the heavy atom which may then be used to calculate the phases of reflections, based on this atom. The remaining atoms are then located by an iterative process by calculation of electron density (Eqn. 1.18) with the observed $|F_{hkl}|$ and phase angles based on known atomic positions (initially the heavy atom only). Careful use of this method results in approximate coordinates of all non hydrogen atoms in the structure.

Application of direct methods results in a knowledge of the phase angles of the reflections with high E values. The usual method of determining the atomic coordinates is from a calculation of an E map using Eqn. 1.18 with $|F_{hkl}|$ replaced by E_{hkl}. It is sometimes possible to determine all non hydrogen atoms from the E map. If this is not the case then the part of the structure obtained from the E map are used to phase the reflections in the same manner as in the heavy atom method.

Further refinement of the structure may be carried out using $|F_{hkl_{(obs)}} - F_{hkl_{(calc)}}|$ as coefficients in Eqn. 1.18, and the phase angle associated with $F_{hkl\ (calc)}$. This ΔF synthesis, Booth 1948 [18], Cochran 1951 [19] is well suited to determination of -

(a) Incorrectly or slightly mis-placed atoms.

(b) Detection of anisotropic thermal motion.

(c) Location of hydrogen atoms.

Interpretation of the ΔF syntheses rests on the observation that if the

proposed structure has assumed an excess of electron content in a given position then this appears as a positive region on the ΔF map, and vice-versa. Thus, grossly misplaced atoms appear as large positive regions with a corresponding negative region in the correct position. The ΔF map contours indicative of anisotropic thermal motion are shown in Fig 2.5.

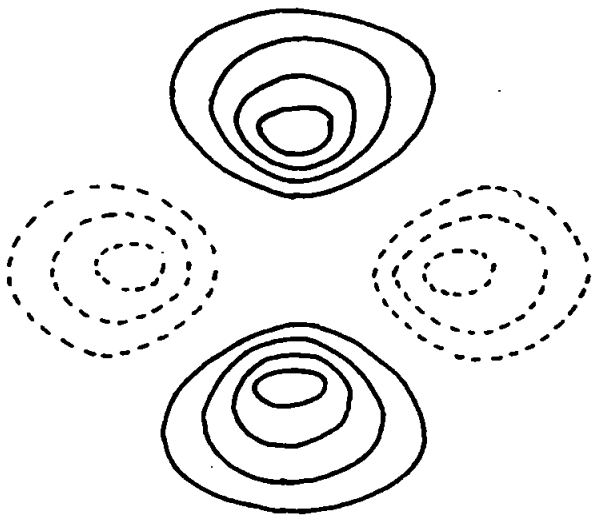


Fig 2.5 ΔF contours showing anisotropic thermal motion.

Hydrogen atom coordinates may be determined from small positive regions of the ΔF synthesis in the regions in which hydrogen atoms are expected. Alternatively it is often convenient to assume the hydrogen atom positions from a knowledge of the average lengths of bonds between hydrogen and other atoms.

2.16 The Residual Index

A measure of the agreement between the measured data and that calculated for the assumed model is provided by the residual index R, where

$$R = \frac{\Sigma(|F_o| - |F_c|)}{\Sigma|F_o|} = \frac{\Sigma\Delta F}{\Sigma F_o} \qquad \text{..... Eqn.2.28}$$

The significance of the R value in early stages of structure solution must be assessed with care, since purely random arrangements of the

correct numbers and species of atoms, in the unit cell, give values of R = 0.83 and R = 0.59 for centric and acentric space groups respectively.

In the latter stages of structure determination, and during the refinement procedure described in the next section, the value of R may be used as an indication of progress. The identification of the last few non hydrogen atoms is usually attended by a marked drop in R.

2.17 Least Squares Refinement

Refinement of the structure consists of determination of the optimum agreement between the observed $F_{o_{hkl}}$ which include errors of measurement and the calculated $F_{c_{hkl}}$ based on the assumed model. The $F_{c_{hkl}}$ based on the approximate parameters x_j y_j z_j, B_j (or U_{11_j} U_{22_j} etc) are given by

$$F_{c_{hkl}} = \sum_{j=1}^{N} f_{o_j} e^{-B_j \sin^2\theta/\lambda^2} \cdot e^{2\pi i(hx_j + ky_j + lz_j)} \qquad \text{..... Eqn. 2.29}$$

For idealised error-free $F_{o_{hkl}}$,

$$F_{o_{hkl}} = \sum_{j=1}^{N} f_{o_j} e^{-(B_j + \Delta B_j)\sin^2\theta/\lambda^2} \cdot e^{2\pi i(h(x_j + \Delta x_j) + k(y_j + \Delta y_j) + l(z_j + \Delta z_j))} \qquad \text{..... Eqn. 2.30}$$

where $B_j + \Delta B_j$, $x_j + \Delta x_j$, $y_j + \Delta y_j$, $z_j + \Delta z_j$, are the correct parameters. For small errors in parameters,

$$F_{o_{hkl}} - F_{c_{hkl}} = \Delta F_{hkl} \qquad \text{..... Eqn. 2.31}$$

and

$$\Delta F_{hkl} = \left[\sum_{j=1}^{N} \frac{\partial F_{c_{hkl}}}{\partial B_j} \cdot \Delta B_j + \frac{\partial F_{c_{hkl}}}{\partial x_j} \cdot \Delta x_j + \frac{\partial F_{c_{hkl}}}{\partial y_j} \cdot \Delta y_j + \frac{\partial F_{c_{hkl}}}{\partial z_j} \Delta z_j \right] \qquad \text{..... Eqn. 2.32}$$

$$\left(\Delta F_{hkl} - \text{R.H.S.} \right) = o \qquad \text{..... Eqn. 2.33}$$

An equation of the form (2.32) may be written for each reflection, but the difference (2.33) is in general non zero, and a least squares

solution must be found for the whole set of equations which minimises the sum of the squares of the differences. The quantity minimised is,

$$D = \sum_{hkl} w_{hkl} (F_{o_{hkl}} - F'_{c_{hkl}})^2 \qquad \text{..... Eqn. 2.34}$$

where $F'_{c_{hkl}}$, the revised value of $F_{c_{hkl}}$ is expressed by,

$$F'_{c_{hkl}} = F_{c_{hkl}} + \left[\Sigma \frac{\partial F_{c_{hkl}}}{\partial B_j} \cdot \Delta B_j + \cdots\cdots \right] \qquad \text{..... Eqn. 2.35}$$

and thus,

$$(F_{o_{hkl}} - F'_{c_{hkl}}) = \Delta F_{hkl} - \left[\Sigma \frac{\partial F_{c_{hkl}}}{\partial B_j} \cdot \Delta B_j + \cdots \right] \qquad \text{..... Eqn. 2.36}$$

The refinement may require a number of cycles for minimisation to be achieved. The improved parameters and $F'_{c_{hkl}}$ from each cycle are used as approximate values for the following cycle, the process being complete when there is no significant change in the parameters between two successive cycles. The application of the method of least squares is discussed in greater detail in ref 4, pp 385 - 398, and by Rollett [20] pp (47-56). As refinement proceeds, the fall in the value of R between successive cycles is a useful indication of the rate of progress.

2.18 Accuracy of Bond Lengths and Angles

Structures of organic compounds are often determined in order to ascertain the electronic or steric environment of particular atoms or groups. The effects of charge delocalisation, steric crowding and ring strain are reflected in abnormal bond lengths and angles. Assessment of the significance of unusual values of these parameters derived from the structure, requires knowledge of their standard deviations.

The error in a function f, related to n uncorrelated variables $x_1\ x_2\ x_3 \cdots x_9$, and derived from them by calculation is given by -

$$\sigma_f = \sqrt{\sum_{j=1}^{n} \left(\frac{\partial f}{\partial x_j}\right)^2 \sigma_j^2} \qquad \text{..... Eqn. 2.37}$$

where σ_j is the standard deviation in x_j.

For a bond between uncorrelated atoms in a monoclinic crystal.

$$\sigma_1 = \sqrt{(\sigma x_1^2 + \sigma x_2^2)\left(\frac{\Delta xa + \Delta zc \cdot \cos\beta}{l}\right)^2 + (\sigma y_1^2 + \sigma y_2)^2}$$

$$\overline{\left(\frac{\Delta yb}{l}\right)^2 + (\sigma z_1^2 + \sigma z_2^2)\left(\frac{\Delta zc + \Delta xa\ \cos\beta}{l}\right)^2} \qquad \text{..... Eqn. 2.38}$$

where x_1 and x_2 are the e.s.d's for atoms 1 and 2 in the x direction and y_1, y_2 and z_1 z_2 have the same meaning for the y and z directions respectively.

For a crystal in a system with orthogonal axes, this expression reduces to -

$$\sigma_1 = \sqrt{(\sigma x_1^2 + \sigma x_2^2)\left(\frac{\Delta xa}{l}\right)^2 + (\sigma y_1^2 + \sigma y_2^2)\left(\frac{\Delta yb}{l}\right)^2 + (\sigma z_1^2 + \sigma z_2^2)\left(\frac{\Delta zc}{l}\right)^2}$$

..... Eqn. 2.39

For isotropic errors, $x_1 = y_1 = z_1$ and $x_2 = y_2 = z_2$ rotation of the axes to place the x axis along the bond direction yields $\Delta x = l$, $\Delta y = \Delta z = o$, and

$$\sigma_1 = \sqrt{\sigma_1^2 + \sigma_2^2} \qquad \text{..... Eqn. 2.40}$$

where σ_1 and σ_2 refer to isotropic σ's

Errors in unit cell parameters cause errors in bond lengths, and the completely general expression for the standard deviation in bond lengths, (ref 4 p 418) includes terms to account for this contribution.

$$\sigma_1 = \sqrt{\left[\sum_{i=1}^{n}\sum_{j=1}^{n}\left(\frac{\partial l}{\partial P_i}\right)\left(\frac{\partial l}{\partial P_j}\right) V_{ij}\right] + \left[\sum_{i=1}^{6}\sum_{j=1}^{6}\left(\frac{\partial l}{\partial a_i}\right)\left(\frac{\partial l}{\partial a_j}\right) V_{ij}\right]}$$

where

l = bond length ..... Eqn. 2.41

P_i P_j are parameters from refinement (positional)
a_i a_j are unit cell parameters.
V_{ij} is related to element b_{ij} of the inverse matrix element of the refinement by -

$$V_{ij} = \left(\sum_{r=1}^{m} \left(\frac{w_r \Delta F_r^2}{m - n} \right) \right) b_{ij}$$

where w_r is the weight of the r^{th} F_o.

ΔF_r is $|Fo_r| - |Fc_r|$

m is the number of F_o's measured.

n is the number of parameters.

$$U_{ij} = \left(\sum_{r=1}^{m^1} -\frac{w_r \Delta \theta_r^2}{m^1 - n^1} \right) b_{ij}$$

where w_r is the weight of the r^{th} θ

$$\Delta \theta_r = \theta_{o_r} - \theta_{c_r}$$

m^1 is the number of measured θ_o's.

n^1 is the number of parameters which define the lattice.

b_{ij} are the elements of the inverse matrix obtained in the refinement of the unit cell parameters.

The expression for the standard deviation in bond angle $\hat{BAC}$, for isotropic errors in position of A, B, C, is

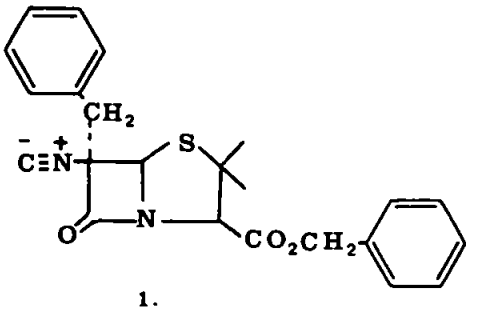
$$\sigma_\theta = \sqrt{\frac{\sigma^2_B}{(AB)^2} + \frac{\sigma_A^2 (BC)^2}{(AB)^2 (AC)^2} + \frac{\sigma^2_C}{(AC)^2}} \qquad \text{..... Eqn. 2.42}$$

where σ_A, σ_B, σ_C are the e.s.d's in positions of atoms A, B, C.

CHAPTER 3

THE CRYSTAL AND MOLECULAR STRUCTURE OF BENZYL 6α - BENZYL 6β - ISOCYANO - PENICILLANATE

(Ref BRL 11827)



1.

3.1 Introduction

The title compound, 1; $C_{23}H_{22}N_2O_3S$ is a representative intermediate in a recently published synthesis of 6α - substituted penicillins - Bentley and Clayton, 1974 [21]. These compounds have been used in structure activity investigations relating to cleavage susceptibility of the β - lactam ring, and may be converted to 7α substituted cephalosporin analogues, via expansion of the thiazolidine ring - Baldwin et al, 1972 [22].

Reports that certain naturally occurring 7α - substituted cephalosporins displayed enhanced activity against gram negative organisms - Stapley et al, 1971 [23a], Nagarajan et al, 1971 [23b], were followed by publication of a number of synthetic routes to 6(7)α - substituted penicillins and cephalosporins. A few of these syntheses are summarized in Appendix A, and an account of previous structure-activity work is given in the next section, followed by details of the structure determination. This work was undertaken principally to confirm chemical evidence for the α-configuration of the benzyl group at C_6.

3.2 Previous Structure-Activity Work on 6(7)α - Substituted Penicillins and Cephalosporins

The chemistry of bacterial cell wall synthesis was investigated by

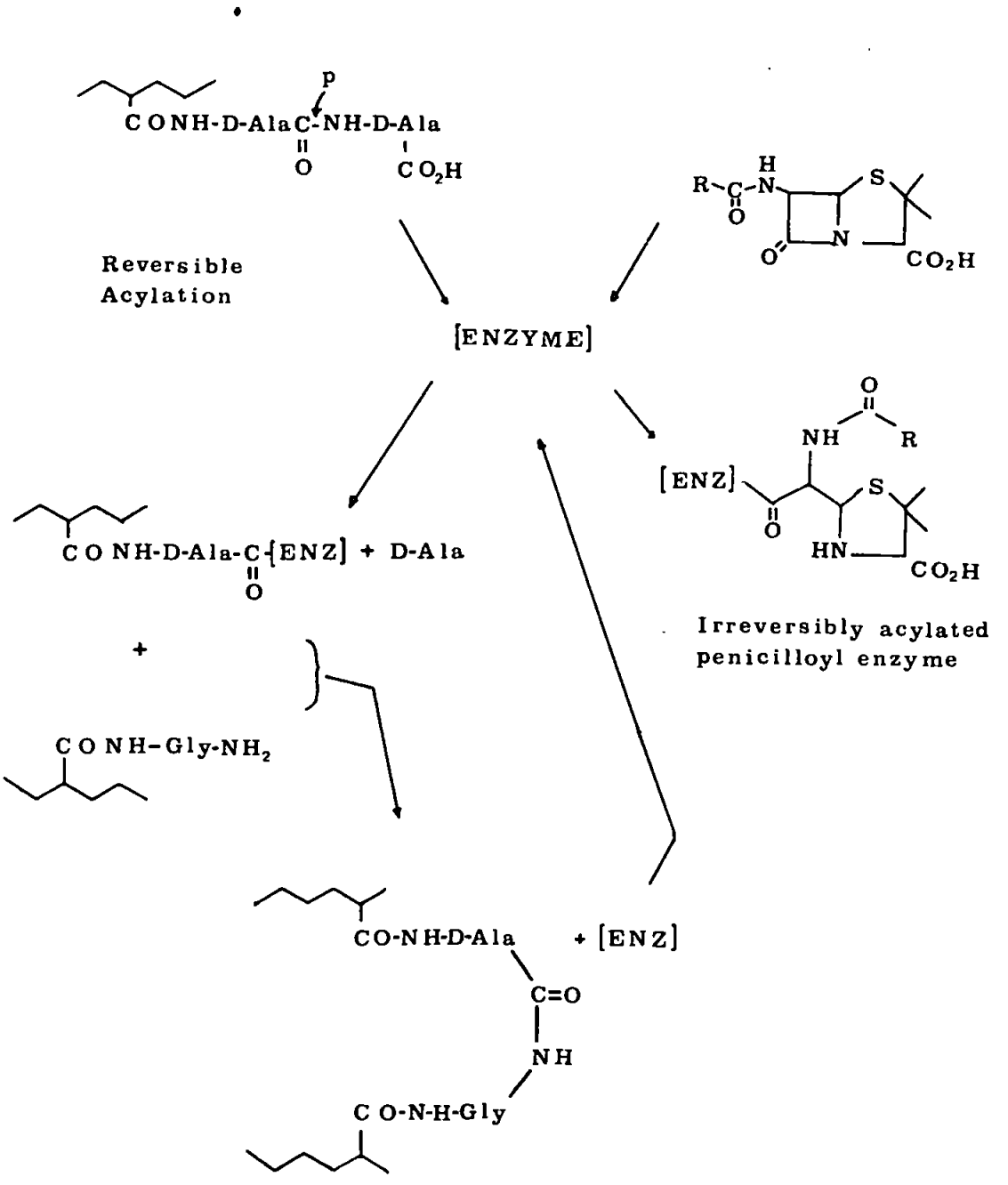
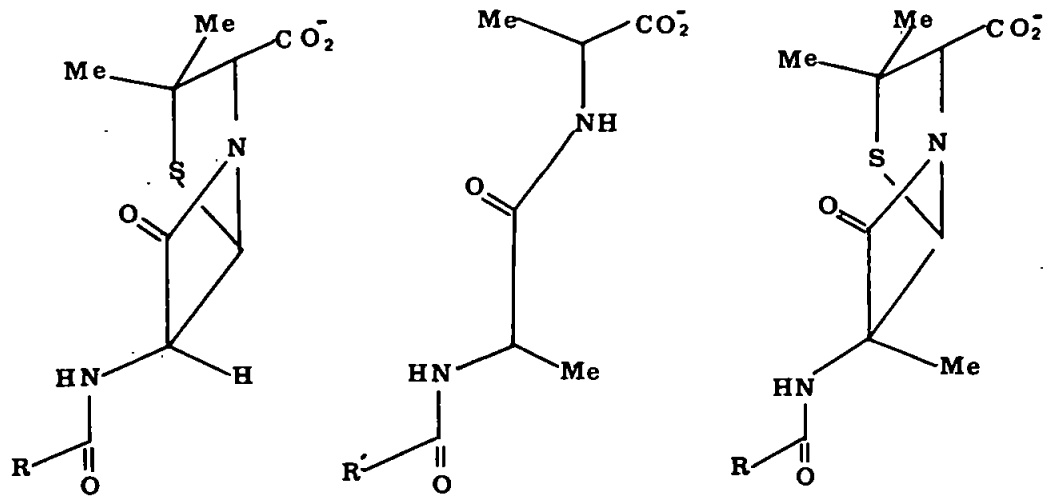


Fig 3·1 Inhibitory mechanism of penicillins.
- Strominger[24].

Strominger et al, 1971 [24] who proposed a mechanism by which β- lactam antibiotics inhibit the final cross linking step. Bacterial cell wall synthesis involves formation of polymeric peptidoglycan strands, the peptide substituents of which are subsequently cross linked via an interpeptide bridge, to yield a three dimensional network. In the important cross linking process, the enzyme transpeptidase is reversibly acylated by the D-alanyl-D alanine end of a tetrapeptide substituent, and one mole of D-alanine is released. The enzyme complex then irreversibly acylates the terminal NH_2 group of a bridging chain attached to the lysine unit in a peptide substituent of another strand. The transpeptidation and the mechanism of inhibition by penicillin proposed by Strominger, are illustrated in Fig 3.1 with peptidoglycan strands represented ⩘ . The effective removal by penicillin of the essential transpeptidase from the cycle, results in loss of mechanical strength of subsequently formed cell walls. Although the longitudinal growth of peptidoglycan strands is relatively unaffected, and cell growth may continue via elongation, the elongated cells have walls which lack the lateral strength derived from the normal macromolecular network. Cell division is severely inhibited, and provided that adequate penicillin concentration is maintained, rupture of the cell wall eventually occurs. The cell contents are then extruded, as a spheroplast which soon bursts under osmotic pressure. For the inhibition to be effective, the penicillin lactam N-C bond must be at least as labile to hydrolysis as the normal peptide link, labelled p on Fig 3.1.

The acceptance at the substrate binding site of transpeptidase, of penicillins was considered by Strominger and Tipper [25] to be due to the structural similarity between them, and D-alanyl - D-alanine in one of its permissible conformations 2a, b. On this basis 6α - methyl penicillins, 2c, which more closely resemble D-alanyl D-alanine were

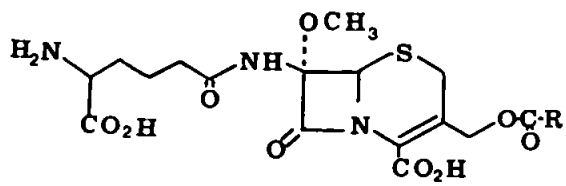
expected to show enhanced activity.



a. b. c.

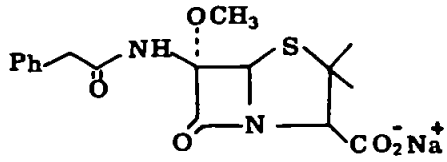
2.

Subsequently a number of 6(7)α alkyl and alkoxy penicillins and cephalosporins were evaluated, and the discovery by Nagarajan et al, [23b] of the naturally occuring 7α - methoxy - cephalosporins 3 focussed attention on synthetic analogues and possible structure activity relationships.

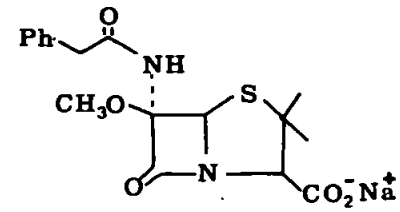


3.

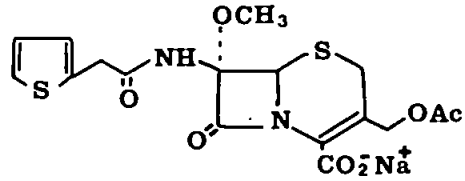
The sodium salts of the epimeric 6-methoxy benzyl penicillins 4a, b, and the 7α - methoxy cephalothin compound 5 were prepared via a stereospecific synthesis by Cama et al, 1971 [26]. Only 5 was active but was of particular interest because it had a spectrum of activity similar to that of cephalothin and also inhibited certain cephalosporin - resistant gram negative organisms.



4a.

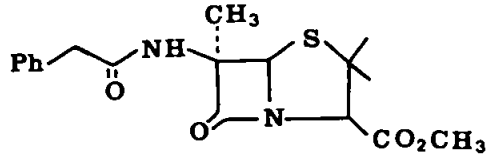


4b.



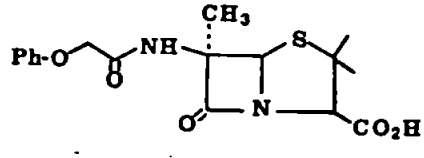
5.

Boehme et al, 1971 [27], confirmed the structure of the inactive methyl ester of 6α - methyl benzyl penicillin, 6 by single crystal X-ray analysis. (Weak activity was however claimed for the free acid, in a later paper by Firestone et al, 1972 [29]).

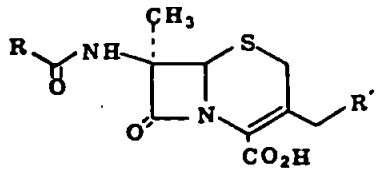


6.

Subsequently, Boehme et al, 1973 [28] prepared the 6(7)α - methyl compounds 7 - 11, of which none exhibited more than 20% of the activity of the corresponding 6(7) α - H compounds, against gram positive organisms. Activity against gram-negative organisms was not observed for 7 - 11 at levels below 200μg/ml.

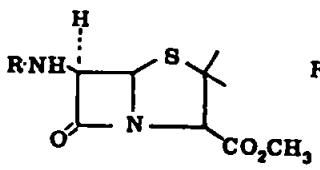


7

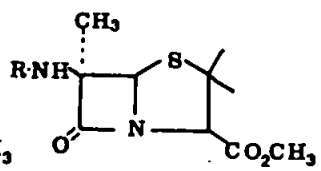


	R	R'
8.	$PhCH_2$-	H
9.	$PhOCH_2$-	H
10.	$PhCHNH_2$-	H
11.	$PhOCH_2$-	OAc

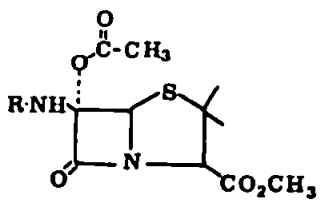
The loss of activity which attended 6α - methyl substitution was thought to result from stabilization of the β- lactam against enzymatically catalyzed nucleophilic attack, and Boehme anticipated that electronegative 6α- substituents would have the reverse effect. A comparison of the rates of basic hydrolysis of 12 - 14 revealed that 14, with the most electronegative substituent was the most easily hydrolyzed.



12.



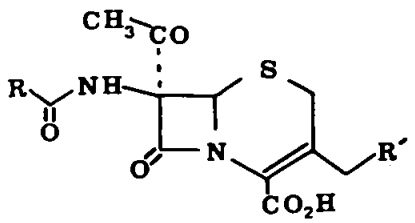
13.



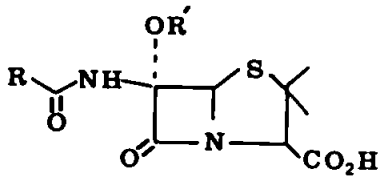
14.

R = $PhOCH_2CO$-

The introduction of substituents of greater electronegativity did not however yield compounds with enhanced antibiotic activity, and the 7α - acetyl cephalosporins 15 - 18 were even less active than the 7α - methyl compounds 8 - 11. Spitzer and Goodson 1973 [30] evaluated the 6(7)α - alkoxy compounds 19 and 20 and the 6(7)α - S - methyl compounds 21 and 22. Of these, only 19a, 20a and 20b had activity exceeding that of the corresponding 6(7)α methyl analogue. Activity levels within 19a - c were observed to decrease sharply with increasing size of the alkoxy



	R	R′
15.	CH_3-	H
16.	$PhCH_2$-	H
17.	$PhOCH_2$-	H
18.	$PhCH_2$-	-OAc



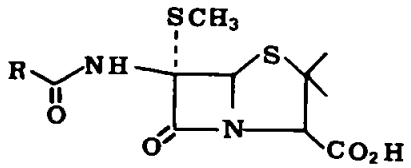
19.

R=$PhOCH_2$-

a. R′=-CH_3

b. R′=-CH_2CH_3

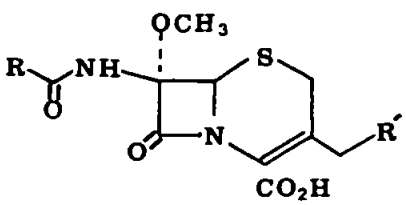
c. R′=-$CH(CH_3)_2$



21.

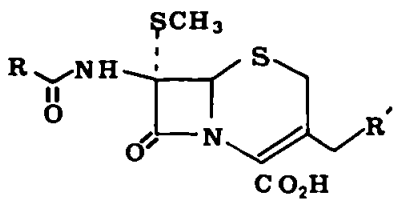
a. R= $PhOCH_2$-

b. R= $PhCH_2$-



20.

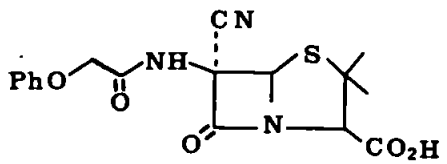
	R	R′
a.	$PhOCH_2$-	H
b.		-OAc



22.

	R	R′
a.	CH_3-	H
b.	$PhOCH_2$-	H
c.		H
d.		-OAc

substituents, and the 6α - S - methyl compounds were all less active than their 6α - methyl counterparts. Weak activity has been reported by Lo and Sheehan, 1975 [31] for the 6α - cyano derivative of penicillin V, 23 and these workers also confirmed the weak activity of 19a.



23.

In summary the results obtained by various workers appear to demonstrate that introduction of 6α substituents does not enhance the activity of penicillins. Most 6- disubstituted compounds are considerably less active than the corresponding 6α - H compounds, and the reduction in activity appears to be related to the size of the substituent group.

Less importance is now attached to the resemblence between penicillins and D-alanyl D-alanine, and Sweet 1972 [32], has suggested that the gross conformational requirements for recognition by transpeptidase of the antibiotic as its substrate, are not very restrictive. The emphasis in more recent structure activity investigations has shifted towards explanation of activity in terms of relative β- lactam resonance stabilization. The effects of geometric factors upon this stabilization are discussed in Chapter 4.

The mechanism of the lysis action of penicillins has recently been investigated by Tomaz and Waks, 1975 [33], who proposed that inhibition of cell wall synthesis by any means triggers bacterial autolytic enzyme release by destabilizing the endogenous complex of an autolysin inhibitor (lipoteichoic acid) and autolytic enzyme, Spratt 1975 [34], offered evidence that the varied effects of β- lactam antibiotics on cell division, elongation and shape, in E. Coli, may be due to the presence of three essential penicillin binding proteins with distinct roles in these processes.

3.3 Space Group and Unit Cell Determination

The crystals used were sections cut from material similar to that illustrated in Plate 1, prepared as in 1.5(i).

Preliminary oscillation and Weissenberg photographs revealed that the compound crystallised in the orthorhombic system and systematic absences at h00 = 2n + 1, 0k0 = 2n + 1, 001 = 2n + 1, indicated space group $P2_12_12_1$ (No. 19). The density measured by flotation in chloroform-cyclohexane was found to be 1,305 kg/m^3. The calculated value for Z = 4 molecules per unit cell, is 1,298 kg/m^3.

Unit cell parameters were determined from calibrated Weissenberg photographs as described in Section 2.3. Refinement of the parameters by least squares analysis of $2\theta_{hkl}$ for ten h0l and twelve 0kl reflections, gave the following values, with e.s.d's in parentheses with respect to the last figures quoted.

$$a = 5.871\ (14) \qquad b = 16.554\ (14) \qquad c = 21.547\ (30)\ \text{Å}$$

3.4 Data Collection and Preliminary Treatment

Multifilm data was collected using the Stoe camera, by the equi-inclination method and CuK_α radiation (λ = 1.54178 Å). Crystals were rotated about the a-axis and data collected for the zero layer and five upper levels. Decomposition of this compound became significant after exposure periods in excess of ten days, and data was therefore collected using three crystals, each being used for only two levels.

The intensities of 2063 reflections were estimated by visual comparison with a calibrated scale, prepared using a range of exposure periods for the 034 reflection. A further 371 reflections were classified as unobserved, 24 were systematically absent and 101 were omitted because they were recorded in regions of excessive background. The intensities were scaled to the top film in each pack, and were subjected to Lp corrections by means of the DATRDN programme of the X-ray 70 system, which also yielded approximate values for the overall isotropic temperature factor B, and the overall scale factor K, from a Wilson plot.

These values were:

$$B = 5.525 \text{ Å}^2 \qquad K = 0.910$$

3.5 Structure Determination and Refinement

The structure was solved by direct methods, using the tangent formula for phase determination. The Frel data were first converted into normalized structure factors, (E's) using the NORMSF programme of the X-ray 70 system, and phase relationships between the 400 reflections of highest E were then derived by the SINGEN programme. The output from SINGEN consists of a list of Σ_2 relationships, in decreasing order of probable validity, in the form

$$\phi h_1k_1l_1 + \phi h_2k_2l_2 + \phi h_3k_3l_3 + \phi \text{shift} = \psi$$

where ψ is approximately zero when the product $Eh_1k_1l_1 \cdot Eh_2k_2l_2 \cdot Eh_3k_3l_3$ is large. ϕ shift is the phase change associated with the transformation of $h_2k_2l_2$ and $h_3k_3l_3$ so that these reflections are asymmetrically equivalent to $h_1k_1l_1$.

In the next stage, phases were assigned to three origin defining reflections and one enantiomorph defining reflection, to conform with the procedures described by Hauptman and Karle 1956 [35], and Karle and Hauptman 1961 [36]. Origin defining reflections were selected from phase-restricted data (0kl h0l hk0 in space group $P2_12_12_1$) in accordance with the requirement that they must be linearly independent as expressed by eqn. 3.1.

$$\begin{vmatrix} h_1 & k_1 & l_1 \\ h_2 & k_2 & l_2 \\ h_3 & k_3 & l_3 \end{vmatrix} = 2n + 1 \qquad \text{.....Eqn. 3.1}$$

The enantiomorph was then defined by selecting a reflection, the sign of the phase of which remained unaltered by the origin translation required in order to change the signs of the origin defining reflections. In

space group $P2_12_12_1$ the enantiomorph defining reflections may be conveniently selected from those reflections having phases restricted to $\pm \frac{\pi}{2}$. The phase change which accompanies an origin translation $\Delta x, \Delta y, \Delta z$, is given by the relationship

$$\Delta\Phi_{hkl} = -2\pi(h \cdot \Delta x + k \cdot \Delta y + l \cdot \Delta z)$$

Within the limits imposed by origin and enantiomorph selection rules, a number of starting sets may be available from reflections of high E, and careful selection is required in order to choose a set which will lead to rapid expansion in the tangent procedure. The best sets consist of reflections which intract among themselves and which enter into many high probability Σ_2 relationships with other reflections of high E.

In this example four apparently equally reasonable starting sets were selected from the 101 reflections of $E \geq 1.94$. The final choice was made after assessment of the relative ease with which each set could be manually expanded within the Σ_2 list to yield phases of 20 - 30 other reflections of high E, using only high probability Σ_2 relationships.

Details of the starting set used are given in Table I which includes the additional 0 0 16 reflection, the phase of which was deduced from a Σ_1 relationship between restricted phases:

Phase restriction:	0/180		0/180		0/180
	Φ 4 0 8	+	$\Phi\bar{4}$ 0 8	-	Φ0 0 16 = 0°

$$\therefore \phi\ 0\ 0\ 16 = 0^\circ$$

TABLE I

Reflection	h	k	l	Φ	E	Number of Σ_2 relationships.
Origin fixing	0	11	7	90°	3.01	191
	1	12	0	90°	2.55	173
	0	4	3	0°	2.37	147
Enantiomorph	0	5	12	90°	2.27	123
Σ_1 determined	0	0	16	0°	2.32	125

The starting set was expanded using the tangent formula, by means of the TANGEN programme of the X-ray 70 System, whereby phases are determined through a series of cycles. Each cycle is defined by the lower limit of E to be used in the iterative phase determination in that cycle. In the first iteration of each cycle, current known phases are used for the estimation of any unknown phases which may be available via Σ_2 relationships, and are above the E threshold for the cycle. Only relationships involving phases above the E limit for the cycle, are used within that cycle. Phases determined in this way are added to the known list, and all are refined. The enlarged and refined list is then employed in the next iteration to obtain further new phase estimates which are in turn included as known and refined. The maximum number of iterations per cycle is 50 but the cycle is terminated prior to this if no further new phases are available above the cycle E limit. The next cycle, with a lower E threshold is then initiated and the iteration sequence is repeated. The maximum number of cycles, and iterations per cycle are at the discretion of the user. The programme is described in detail in the X-ray 74 System, pp 186 - 192.

The progress of the determination is illustrated in Table II in which it may be seen that the first cycle of nine iterations yielded 103 of the 391 phase estimates obtained for reflections of $E \geqslant 1.38$.

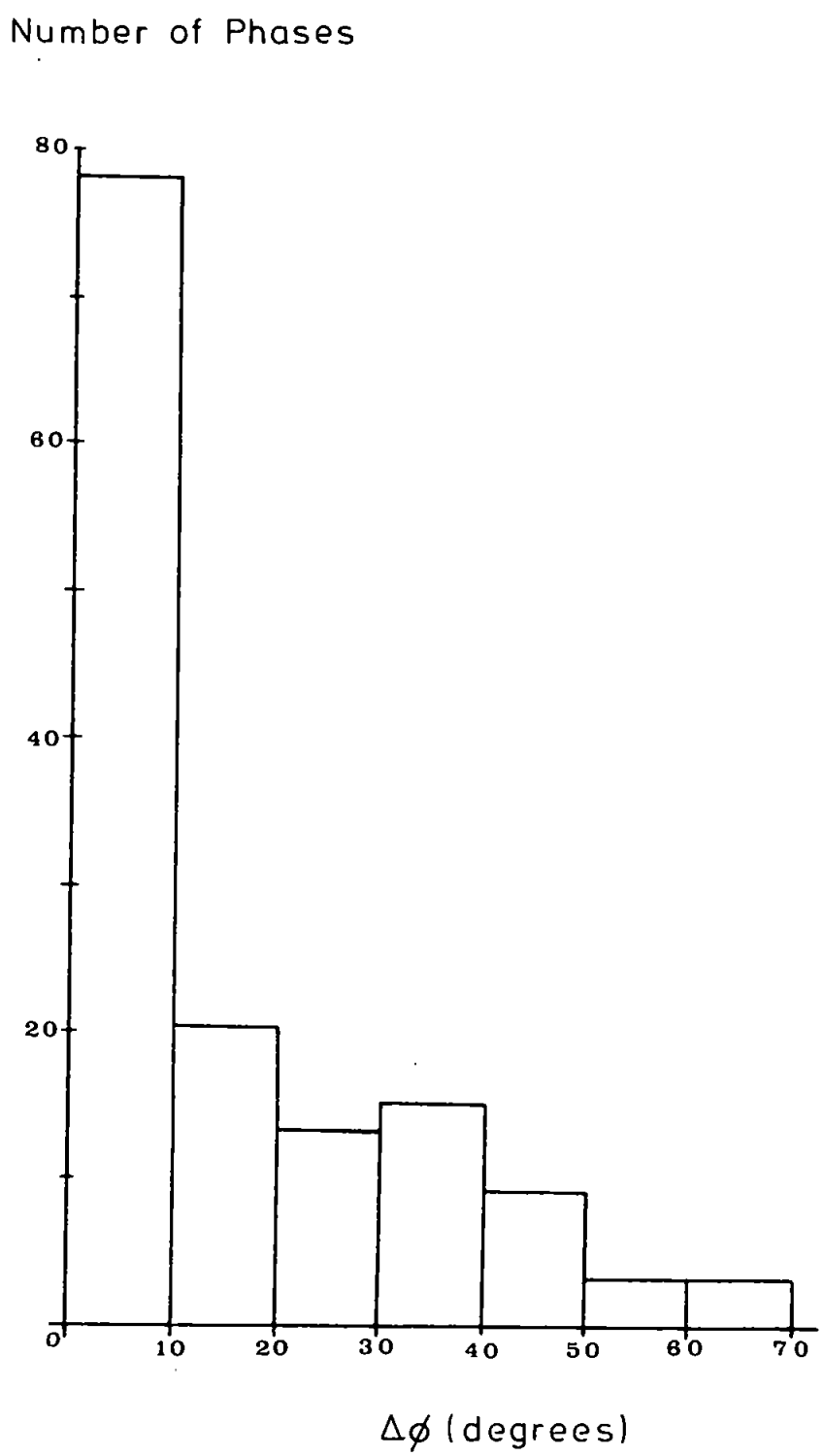


Fig 3·2 - Deviation from final phase values for refined structure.

Table II. Expansion of the Phase Set

Cycle	Number of Iterations	$E \geq$	Phases determined in cycle
1	9	1.90	103
2	7	1.80	21
3	19	1.70	37
4	4	1.60	70
5	21	1.50	63
6	21	1.43	49
7	4	1.38	43

All phases determined from the tangent formula were found to be multiples of $\pi/2$. The reason for this is that only reflections with high E values were used in the phase determining procedure and these contain a large scattering contribution from the sulphur atom. The sulphur atom was subsequently determined to be near the origin. The agreement between the phase estimates from the tangent formula and the final values for the refined structure is illustrated in Fig 3.2. Of the 150 reflections of highest E, 99 had refined phases within 20° of the tangent estimated values. An E map based on these phased reflections revealed the positions of the 18 non hydrogen atoms shown in Fig 3.3a. The usual Fourier technique using the known atomic positions to phase the observed F_o, was used to determine the positions of the remaining atoms. Two syntheses were required for completion of the structure, the remaining atoms being located in the order indicated in Fig 3.3b, c.

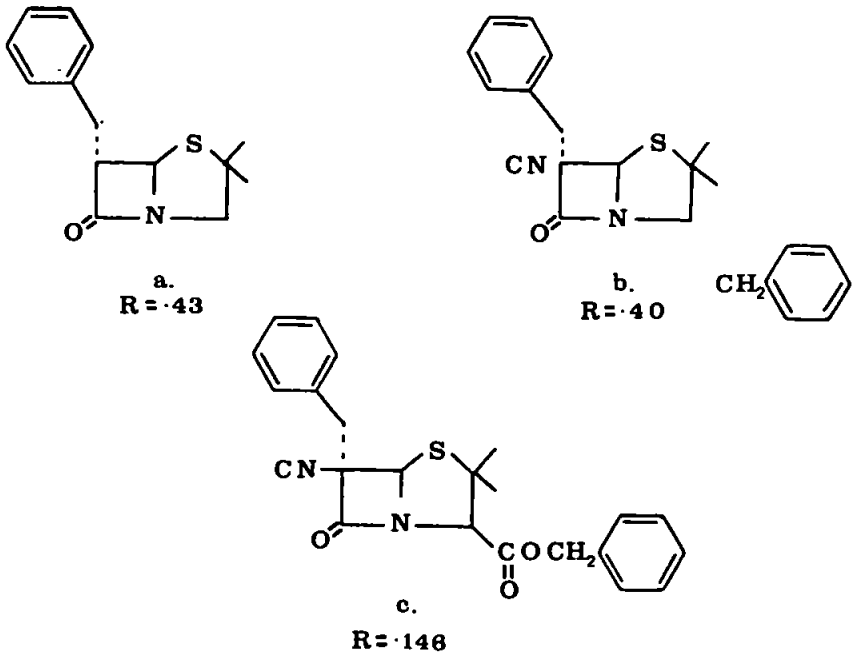


Fig 3·3

Least squares refinement lowered the value of R (unweighted) to 0.146 for the structure with no hydrogen atoms included. Allowance for anisotropy of the sulphur atom, evident in a difference map, and application of a weighting scheme, $w = \frac{1}{[\Delta F]^2}$ where $F = 0.066F_o + 0.746$, lowered the R factor to R (weighted) = 0.131. The weighting scheme was derived graphically from a least squares plot of $\overline{\Delta F}$ vs F_o for six ranges of F_o utilizing ΔF values for all six levels of data.

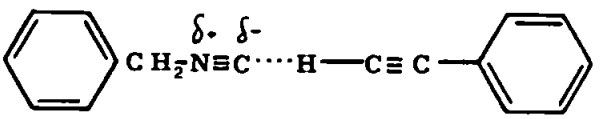
As hydrogen atoms could not be located and no clear indications of further anisotropy could be seen on a difference map, intensity measurements of greater accuracy were considered necessary for satisfactory refinement. Microdensitometer intensity data was

collected for 1494 unique reflections, at the S.R.C. Microdensitometer Service Facility at Chilton. The intensities were subjected to L_p corrections and converted into F_o by means of the HKLF and MERG sections of the SHEL-X programme, [17]. Using these new F_o values the structure was initially refined to R = 0.099 after two cycles of full matrix least squares refinement. A difference map revealed 17 of the 22 hydrogen atoms and a further 2 cycles of least squares refinement, with benzene rings and methyl groups refined as rigid groups, with C - H constrained to be 1.08 Å lowered the unweighted R factor to 0.090. Finally, all non hydrogen atoms except benzene carbons were refined anisotropically with all hydrogen atoms at their calculated positions, constrained to ride on carbon atoms. The values of U_{11} were constrained to equal the mean of U_{22} and U_{33}, as data had been collected along the a-axis. Interlayer scale factors were refined throughout. The final value of the unweighted R factor was 0.077, which was considered acceptable in view of the partial decomposition of the crystals during exposure to X-rays. Structure factor tables for the isocyano compound are listed in Appendix B.

3.6 Discussion of the Structure

The final positional and thermal parameters of the isocyano compound are listed in Tables III and IV. Bond lengths and angles are listed with their e.s.d's in parentheses with respect to the last figures given, in Tables V and VI and are illustrated in Figs 3.4 and 3.5. A projection of the structure as viewed along the a-axis is shown in Fig 3.6 in which perspective has been represented by enlargement of near atoms.

Isocyano groups are very dipolar and C···H···C hydrogen bonding has been reported between benzyl isonitrate and phenylacetylene, Ferstandig, 1962 [37]. The acetylenic hydrogen in this



case, is very acidic, and it seems unlikely that there is significant interaction between the isocyano carbon C_{29} of the penicillanate, and the nearest hydrogen of another molecule, which is the benzenoid hydrogen HC_{27}, at a distance of 2.83Å from C_{29}. The isocyano groups in different molecules appear to be too distant to interact with each other. The minimum N···C separation for these groups in molecules related by the 2_1 axis along a, is 4.39Å.

Penicillins derived from this compound and other 6α subsituted analogues were found to display no significant antibacterial activity. In order to ascertain whether increased β-lactam resonance stabilization might be responsible for the lack of activity the detailed geometry of the lactam system was investigated. A stronger N_4-C_7 bond would result from resonance stabilization involving delocalization of N_4 lone pair electrons, with consequent reduction of the acylating power of the penicillin towards the transpeptidase enzyme. A reduction in acylating power would render the penicillin less effective in deactivating the

TABLE III

Positional and thermal parameters for the non-hydrogen atoms of ERL 11827 obtained from final least squares refinement.

Positional parameters are given as fractions of cell edges x 10^4.

Isotropic temperature factors are of the form exp $(-B \sin^2 \theta/\lambda^2)$.

Anisotropic temperature factors are expressed as -

$$\exp\left[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)\right]$$

The units of B are Å^2 x 10^2 and those of U_{ij} are Å^2 x 10^4.

Standard deviations in parentheses are with respect to the last figure given.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	66(3)	5218(2)	4940(1)	566(9)	550(14)	596(16)	-55(15)	97(11)	46(11)
C2	2654(12)	5828(6)	4991(5)	536(23)	509(57)	562(58)	-79(57)	20(43)	161(37)
C3	3928(14)	5662(6)	4381(5)	539(25)	456(58)	622(64)	-141(56)	-13(45)	-83(41)
N4	3390(10)	4860(5)	4201(3)	433(19)	374(41)	494(43)	11(41)	24(26)	-97(33)
C5	1109(13)	4576(6)	4343(5)	478(23)	421(56)	536(54)	97(54)	110(37)	-40(40)
C6	2190(12)	3717(6)	4484(5)	471(23)	269(52)	671(63)	17(54)	113(43)	-3(37)
C7	4423(13)	4170(6)	4391(5)	443(25)	377(57)	511(61)	60(53)	54(35)	-91(36)
C8	6368(10)	3979(4)	4449(4)	600(21)	411(41)	796(48)	-50(41)	-11(32)	6(29)
C9	1951(18)	6661(8)	5127(7)	862(38)	631(77)	1092(91)	-105(83)	203(45)	117(62)
C10	4096(18)	5511(9)	5516(6)	787(34)	989(93)	586(76)	-100(84)	-58(54)	-89(61)

continued···

TABLE III (continued)

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C11	3258(15)	6260(7)	3868(6)	616(26)	490(61)	740(68)	-1(64)	-27(48)	-42(50)
O12	4109(13)	6919(5)	3825(5)	966(29)	540(50)	1387(69)	129(56)	-156(48)	-235(41)
O13	1694(10)	5965(5)	3500(3)	666(21)	576(43)	754(47)	166(40)	-173(33)	-113(31)
C14	1019(21)	6505(9)	3002(7)	1006(46)	967(100)	1043(108)	399(96)	-326(73)	-36(75)
C15	9275(11)	6048(5)	2616(4)	673(10)					
C16	9312(11)	6121(5)	1974(4)	782(34)					
C17	7642(11)	5761(5)	1619(4)	1041(45)					
C18	5934(11)	5328(5)	1906(4)	1043(42)					
C19	5897(11)	5254(5)	2547(4)	971(38)					
C20	7567(11)	5614(5)	2902(4)	794(34)					
C21	1495(16)	3013(7)	4061(5)	622(28)	585(68)	659(71)	-178(58)	-11(44)	-11(45)
C22	1916(8)	3187(5)	3382(3)	519(23)					
C23	237(8)	3530(5)	3021(3)	736(30)					
C24	570(8)	3634(5)	2388(3)	846(36)					
C25	2580(8)	3394(5)	2117(3)	896(40)					
C26	4259(8)	3051(5)	2479(3)	838(36)					
C27	3927(8)	2947(5)	3112(3)	696(29)					
N28	1948(11)	3481(6)	5117(5)	614(22)	573(57)	653(58)	128(53)	139(44)	-34(36)
C29	1796(17)	3288(8)	5628(7)	806(34)	757(86)	853(90)	-51(85)	130(68)	44(63)

TABLE IV

Coordinates of hydrogen atoms of BRL 11827 given as fractions of cell edges $X10^4$ with standard deviations in parentheses

ATOM	x	y	z
H C (3)	5702 (14)	5740 (6)	4456 (5)
H C (5)	9645 (13)	4567 (6)	4051 (5)
H C (9) (I)	1023 (18)	6875 (8)	4732 (7)
C (9) (II)	3447 (18)	7018 (8)	5184 (7)
C (9) (III)	0927 (18)	6711 (8)	5536 (7)
H C (10) (I)	4836 (18)	4922 (9)	5470 (6)
C (10) (II)	3035 (18)	5524 (9)	5920 (6)
C (10) (III)	5403 (18)	5955 (9)	5564 (6)
H C (14) (I)	1602 (21)	6430 (9)	2534 (7)
C (14) (II)	9552 (21)	6884 (9)	3004 (7)
H C (16)	10634 (11)	6456 (5)	1752 (4)
H C (17)	7670 (11)	5817 (5)	1122 (4)
H C (18)	4641 (11)	5049 (5)	1631 (4)
H C (19)	4575 (11)	4919 (5)	2769 (4)
H C (20)	7538 (11)	5558 (5)	3399 (4)
H C (21) (I)	9896 (16)	2975 (7)	3830 (5)
H C (21) (II)	2678 (16)	2622 (7)	3833 (5)
H C (23)	8680 (8)	3715 (5)	3230 (3)
H C (24)	9270 (8)	3899 (5)	2108 (3)
H C (25	2838 (8)	3475 (5)	1628 (3)
H C (26)	5816 (8)	2866 (5)	2270 (3)
H C (27)	5226 (8)	2682 (5)	3392 (3)

TABLE V

Bond distances for ERL 11827 with their standard deviations (Å) after final least squares refinement. Atoms C(15) - C(20) and C(22) - C(27) were refined as rigid phenyl groups with C - C distances of 1.395 Å .

S(1) - C(2)	1.828 (6)
S(1) - C(5)	1.777 (7)
C(2) - C(3)	1.537 (9)
C(3) - N(4)	1.419 (8)
N(4) - C(5)	1.452 (7)
C(5) - C(6)	1.587 (8)
C(6) - C(7)	1.524 (8)
N(4) - C(7)	1.357 (8)
C(2) - C(9)	1.469 (10)
C(2) - C(10)	1.507 (10)
C(3) - C(11)	1.535 (10)
C(11)- O(12)	1.203 (9)
C(11)- O(13)	1.308 (8)
C(7) - O(8)	1.191 (6)
C(6) - N(28)	1.426 (9)
C(6) - C(21)	1.535 (10)
N(28)- C(29)	1.150 (9)
O(13)- C(14)	1.452 (9)
C(14)- C(15)	1.521 (10)
C(21)- C(22)	1.511 (9)

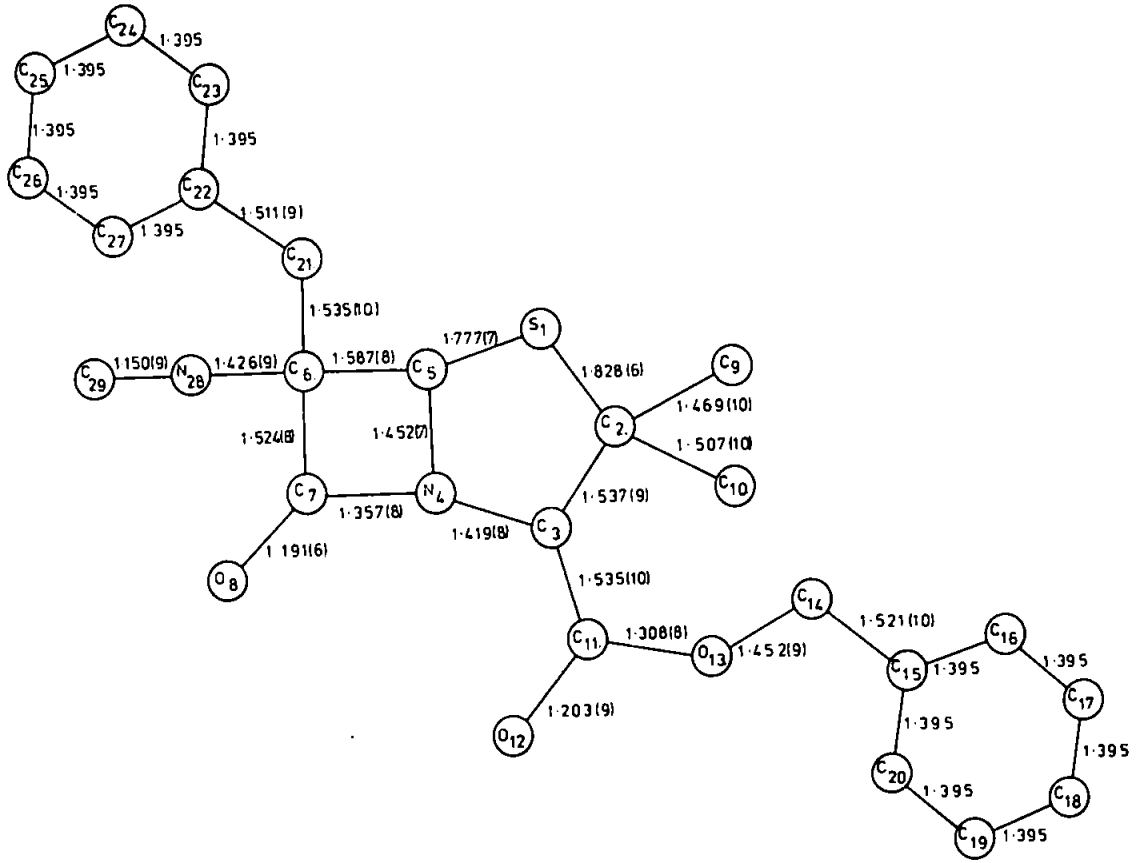


Fig 3·4 – Bond distances for the isocyanopenicillanate, BRL 11827. (Å)

TABLE VI

Bond angles and their standard deviations (^{o}) for BRL 11827 Interbond angles within the phenyl groups C(15) - C(20) and C(22) - C(27) were assumed to be 120^{o}.

C(5) - S(1) - C(2)	95.0 (0.3)
S(1) - C(2) - C(3)	104.7 (0.4)
C(2) - C(3) - N(4)	107.0 (0.5)
C(3) - N(4) - C(5)	116.8 (0.5)
C(3) - N(4) - C(7)	127.3 (0.5)
N(4) - C(5) - S(1)	106.1 (0.4)
S(1) - C(5) - C(6)	122.3 (0.5)
N(4) - C(5) - C(6)	87.8 (0.4)
C(5) - C(6) - C(7)	83.0 (0.4)
C(6) - C(7) - N(4)	94.0 (0.4)
C(7) - N(4) - C(5)	94.4 (0.4)
S(1) - C(2) - C(9)	107.3 (0.4)
S(1) - C(2) - C(10)	108.7 (0.5)
C(3) - C(2) - C(10)	107.8 (0.5)
C(9) - C(2) - C(10)	109.6 (0.7)
C(3) - C(2) - C(9)	118.4 (0.6)
C(2) - C(3) - C(11)	112.1 (0.5)
N(4) - C(3) - C(11)	110.5 (0.5)
C(3) - C(11)- O(12)	122.3 (0.6)
C(3) - C(11)- O(13)	112.1 (0.6)
O(12)- C(11)- O(13)	125.7 (0.7)
C(11)- O(13)- C(14)	114.2 (0.6)
C(13)- C(14)- C(15)	106.4 (0.4)

TABLE VI (continued)

C(14) - C(15) - C(16)	119.4 (0.4)
C(14) - C(15) - C(20)	120.3 (0.4)
N(4) - C(7) - O(8)	133.1 (0.5)
C(6) - C(7) - O(8)	132.9 (0.6)
C(5) - C(6) - N(28)	112.9 (0.5)
C(6) - N(28) - C(29)	178.7 (0.6)
C(7) - C(6) - N(28)	110.3 (0.5)
C(5) - C(6) - C(21)	117.4 (0.6)
C(7) - C(6) - C(21)	121.6 (0.5)
C(21) - C(6) - N(28)	109.5 (0.5)
C(6) - C(21) - C(22)	112.8 (0.6)
C(21) - C(22) - C(23)	120.5 (0.3)
C(21) - C(22) - C(27)	119.7 (0.3)

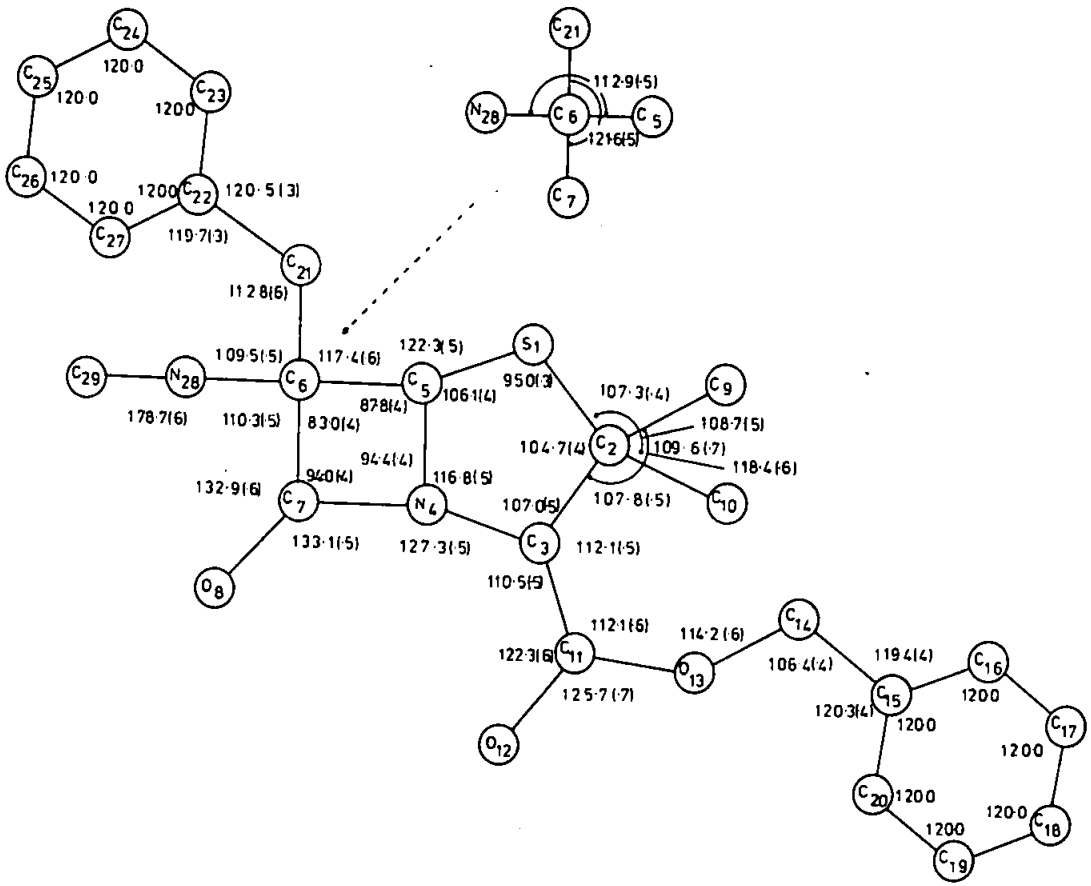


Fig 3·5 – Bond angles for the isocyanopenicillanate, BRL 11827.

(degrees)

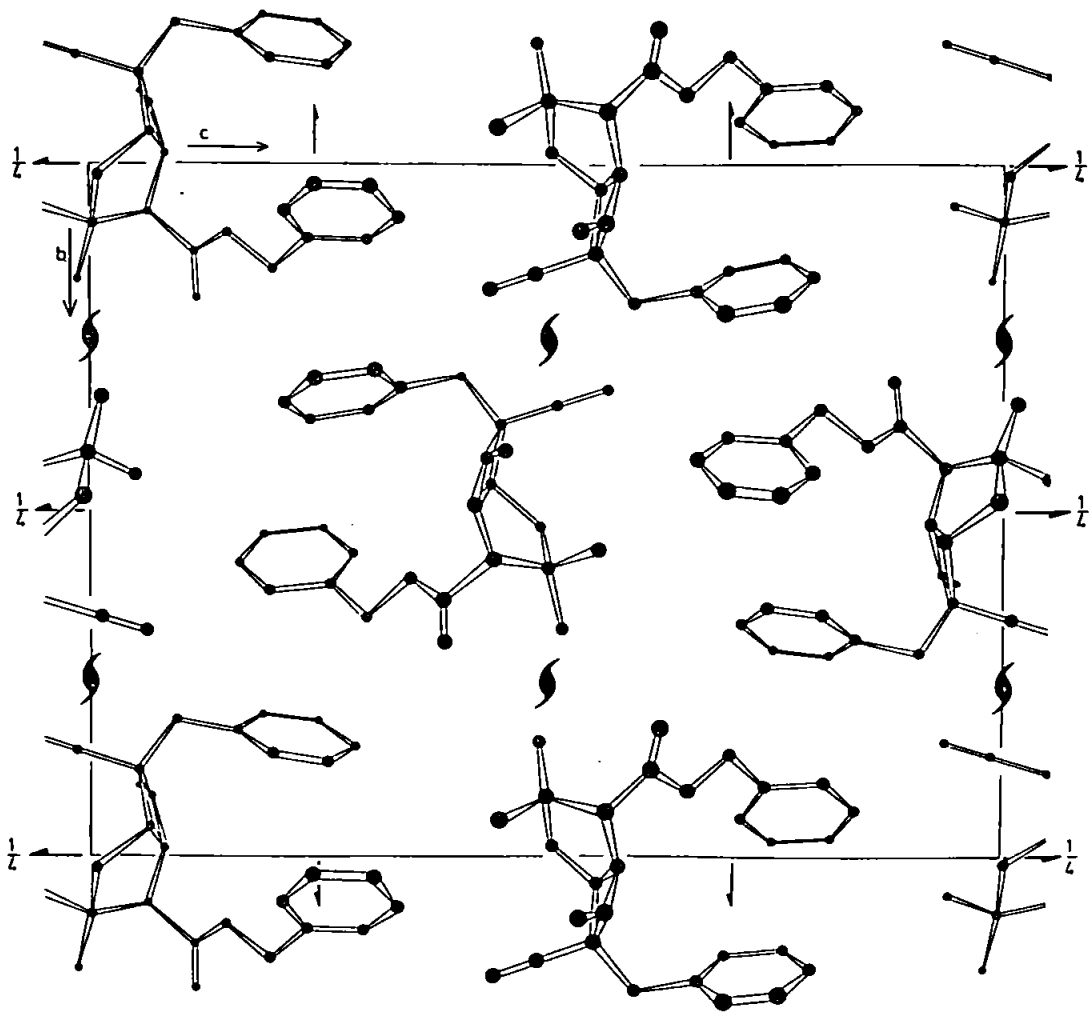


Fig 3·6 Structure of the isocyanopenicillanate BRL 11827 as viewed from the direction of the a-axis

enzyme. Maximum resonance stabilization requires coplanarity of the atoms involved so that π orbital overlap is optimized, as illustrated in Fig 3.7 which represents normal amide resonance. Therefore, in addition to information derived from bond lengths, it is necessary to ascertain the degree of coplanarity of N_4 with its substituent atoms. β-lactam resonance is discussed in more detail in section 4.3.

a. Deviation of N_4 from substituent plane:

By means of least squares plane calculation the distance of N_4 above the plane of C_3 C_5 and C_7 was obtained. These three atoms define a plane $Px + Qy + Rz = S$ in direct space where $P = 0.307$, $Q = 0.043$, $R = 21.518$ and $S = 9.336$. The nitrogen atom was found to be 0.37Å from the plane of the substituent atoms, this value being within the range of those reported for the active penicillins listed in Table VII. Bond lengths for $N_4 - C_7$ and $C_7 - O_8$, and the sum of bond angles about N_4 are also comparable with those of active compounds.

TABLE VII β - lactam structural parameters

Compound	Sum of angles about N_4(°)	Deviation of N_4 from plane of C_3-C_5-C_7(Å)	Bond Lengths (Å) N_4-C_7	C_7-O_8	Source
ampicillin anhydrate	338	0.35	1.385	1.176	1
ampicillin trihydrate	337	0.38	1.460	1.210	2
penicillin V	339	0.40	1.360	1.198	2
6-A.P.A.	343	0.32	1.392	1.228	2
isocyano intermediate	339	0.37	1.367	1.211	3

1. Boles and Girven 1976 [3].
2. Sweet 1970 [32b].
3. This work.

There is therefore no evidence of unusual β-lactam amide stabilization relative to active penicillins, and the 6α- alkyl 6 β- acylamino

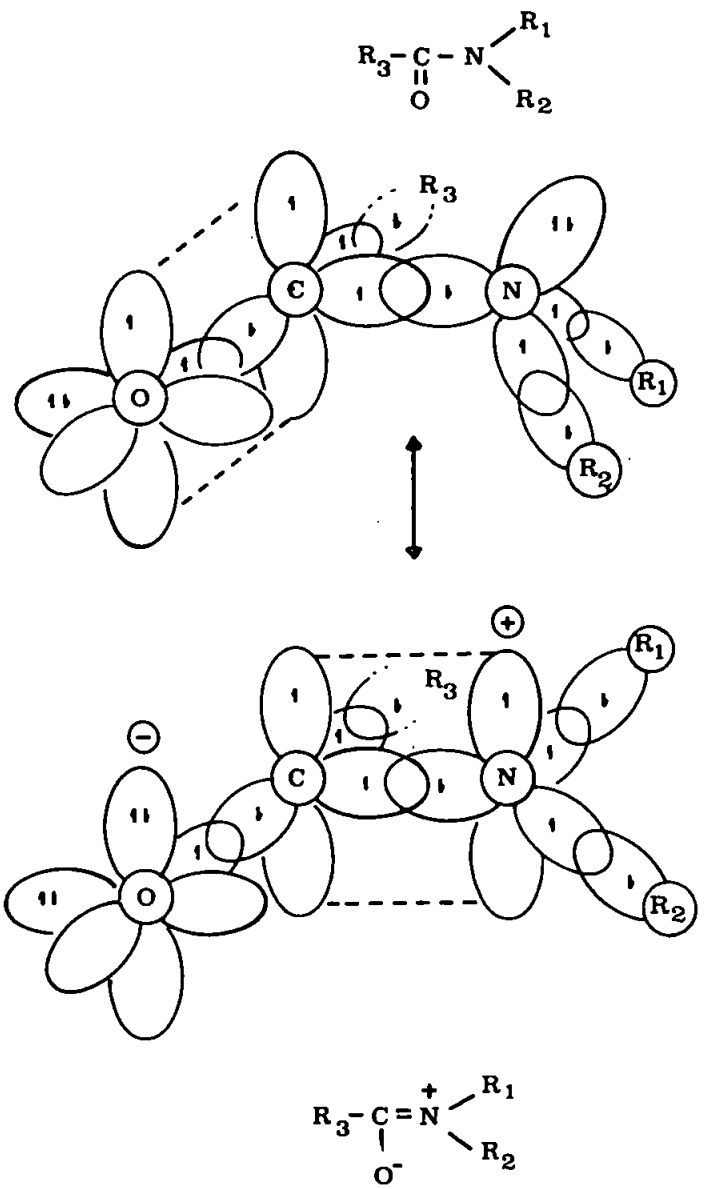


Fig 3·7 Amide resonance

penicillanates derived from the isocyano compound must be inactive for chemical reasons associated with the 6β- substituent. That the electronegativity of this group would not be of particular significance is indicated by the results of Boehme, discussed in section 3.2. Lactam resonance is discussed in more detail in Chapter 4.

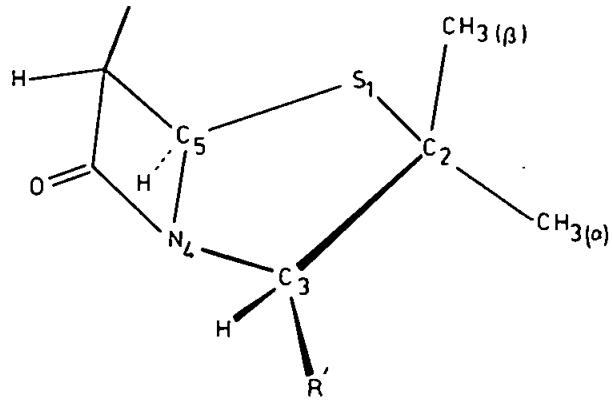
b. The thiazolidine ring:

In order that the substituents at C_2 and C_3 do not eclipse one another, the thiazolidine ring of penicillins must assume a conformation in which four of the atoms are almost coplanar, and the fifth atom is out of plane. This is illustrated in Fig 3.8 which shows the two possible conformations and also the distance by which the specified atom deviates from the least squares plane of the other four. Four of the five compounds of Type A have C_3 below the plane of S_1 C_2 N_4 and C_5, while two of the three of Type B have S_1 above the plane of the other atoms.

In the isocyano compound C_3 lies 0.45Å below the least squares plane of S_1 C_2 N_4 and C_5. This plane is expressed in direct space in the form $Px + Qy + Rz = S$, where P = 2.174, Q = 0.043, R = 21.518 and S = 9.330, and the defining atoms lie at the following distances from the plane

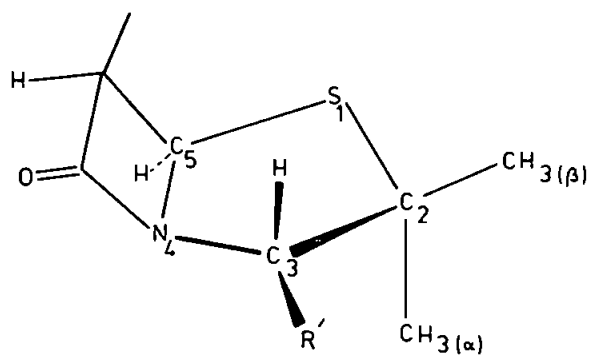
Atom	Distance from L.S. plane (Å)
S_1	- 0.004
C_2	0.003
N_4	- 0.004
C_5	0.005

The deviation of C_3 from the plane of the other thiazolidine ring atoms is of the same order as that in penicillin V, p-bromo-penicillin V, and potassium benzyl penicillin.



TYPE A :-

			ref.
PHENOXYMETHYL-PENICILLIN penicillin-V	C_3 down	0·51 Å	39
6-AMINO-PENICILLANIC ACID	N_4 up	0·4 Å	40
p-BROMOPENICILLIN V	C_3 down	0·4 Å	41
POTASSIUM BENZYL PENICILLIN penicillin-G	C_3 down	0·5 Å	42
ISOCYANO INTERMEDIATE	C_3 down	0·45 Å	



TYPE B :-

AMPICILLIN ANHYDRATE	C_2 down	0·71 Å	3
AMPICILLIN TRIHYDRATE	S_1 up	0·84 Å	32b

Fig 3·8 - Thiazolidine ring conformations in some penicillins of known structure.

Other Bond Lengths:

Apart from the rused ring system, the other parts of the molecule which are of interest are the isocyano -NC and ester $\rangle C=O$ functions. The values for $\overset{+}{N} \equiv \overset{-}{C}$ and ester $\rangle C=O$ distances are in fair agreement with those given in International Tables for X-ray Crystallography, Vol 3, 1968.

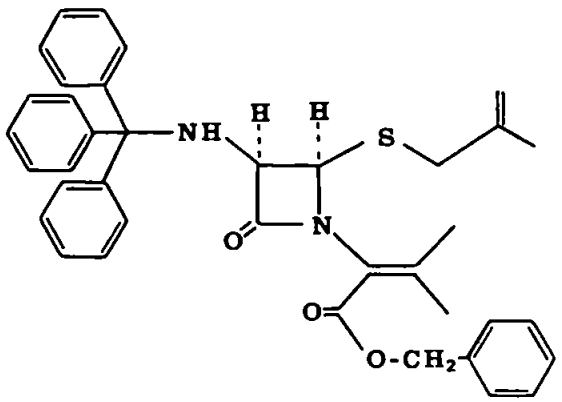
	Int. Tables	Isocyano Cpd
$R - C \equiv N$	1.158 ± 2 Å	1.155Å
$R - \underset{\vert}{C} = O$	1.230 Å	1.213Å

Conclusion

The isocyano intermediate is similar in terms of conformation and bond lengths, to several active penicillins, and the benzyl group at C_6 has the α- configuration, as expected from chemical evidence as summarized in Appendix A, scheme 6. It therefore seems reasonable to propose that the reduction in activity which follows the introduction of a 6α- substituent is not associated with any significant change in β- lactam resonance stabilization. The results of other workers which were discussed in section 3.1 appear to indicate that the size of the substituent may be important in relation to the lowering of activity.

CHAPTER 4

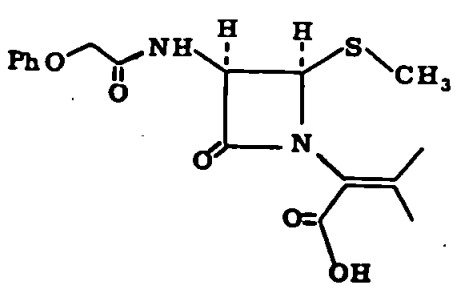
The Crystal and Molecular Structure of - (3R, 4R)-1-(1-benzyloxycarbonyl -2-methyl-prop-1-enyl)-4-(β-methylallylthio)-3(triphenylmethyl-amino) - azetidin-2-one (Ref E.B.976)



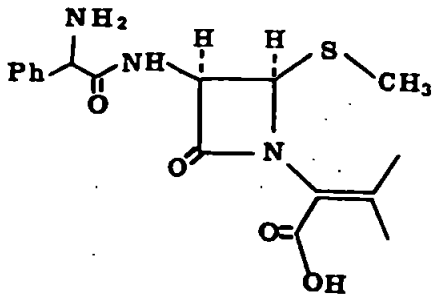
1.

4.1 Introduction

The seco-penicillin 1, $C_{38}H_{38}N_2O_3S$, belongs to a group of monocyclic β-lactams, prepared by Brain et al, 1975 [48] by the base catalysed intermolecular S-alkylation of benzyl 6β- tritylamino-penicillanate. Selective cleavage of the 1 - 2 bond of the thiazolidine ring accompanies alkylation, but the β- lactam ring remains intact. The resistance of the β- lactam to cleavage by either potassium t-butoxide, or powdered sodium hydroxide, during the alkylations indicates a reduced susceptibility to nucleophilic attack relative to that of fused ring β- lactams. Hydrolytic removal of the trityl group (Ph_3C-) from 1 and its analogues, yields the corresponding 3 - amino-azetidin-2-one, which may then be acylated in the same way as 6-amino penicillanic acid. Hydrogenolysis of the ester benzyl group then affords the free acid. Monocyclic analogues 2 and 3 of penicillin V and ampicillin respectively were thus prepared by Brain, but were found to possess no significant antibiotic activity.



2.



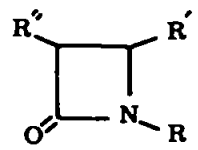
3.

The structure determination of 1 was undertaken to ascertain both the geometry of the bonding of the lactam ring, and the extent by which the nitrogen of the ring deviates from the plane of its substituent atoms. The importance of these features is discussed in the following section.

4.2 Previous Work

Only infrequently have monocyclic lactams been found, which possess anti-bacterial activity but those which have been reported are of particular interest since the activity is not confined to compounds closely related to penicillins. For example, Bose et al 1974 [49], evaluated 18 synthetic 1, 3, 4,-trisubstituted azetidin-2-ones, and detected activity of a lower order than most penicillins or cephalosporins, in compounds 4 (overleaf).

Instead of an acylamino function, most of these compounds have phenoxy or methoxy substituents at C_3. The structure activity relationships of this group appear to be different from those of fused ring lactams. When the active 3-NH_2 compound was phenacetylated, the product was found to be inactive, while compounds 4 f and g were active but of trans-configuration.

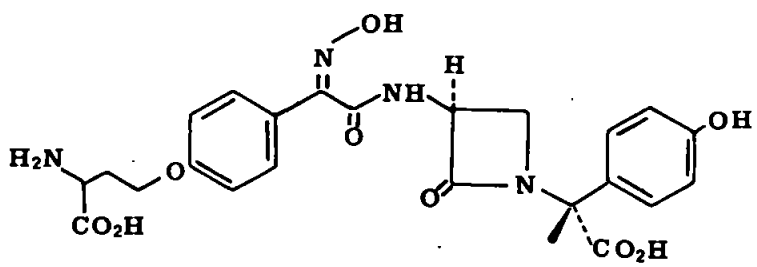


4.

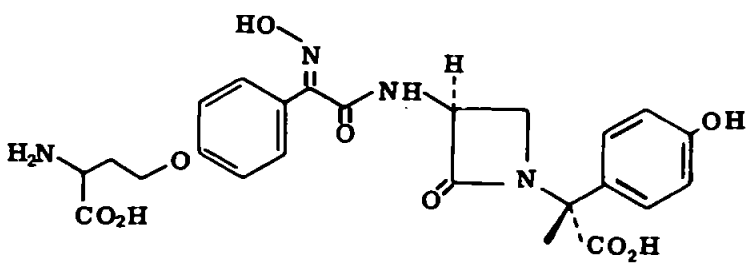
	R	R′	R″
a.	diphenylmethyl	p-anisyl	methoxy
b.	diphenylmethyl	p-anisyl	amino
c.	cyclohexyl	o-nitrophenyl	methoxy
d.	cyclohexyl	o-aminophenyl	phenoxy
e.	cyclohexyl	o-phenylacetamido o-phenyl	phenoxy
f.	p-anisyl	p-carboxyphenyl	phenoxy
g.	p-carboxyphenyl	2-furyl	phenoxy
h.	phenyl	o-aminophenyl	phenoxy

(f and g, trans, others cis)

In contrast to these compounds, are the very active nocardicins A and B, 5a, b isolated and characterised by Hashimoto et al, 1976 [50].



5a.



5b.

These compounds, which are the first examples of monocyclic β-lactams of high potency, have the same steriochemistry as penicillins, and were

reported to be enzyme inhibitors of the cell wall synthesis of bacteria. Although seco penicillins are inactive, they may be used to provide access to a number of derived compounds. Permanganate oxidation of the N_1 substituent for example, yields the NH compound, which may then be alkylated, as in Fig 4.1, Nayler et al, 1973 [51].

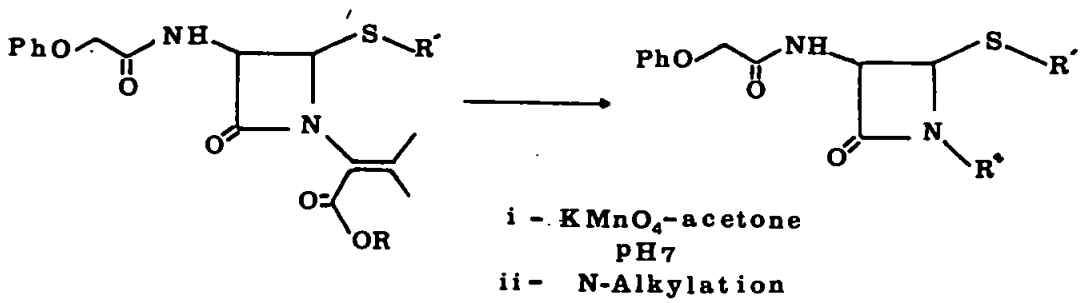


Fig 4·1

In certain cases, cyclization to a cephem sulphone may be achieved, as illustrated in Fig 4.2, Yashimoto et al, 1972 [52].

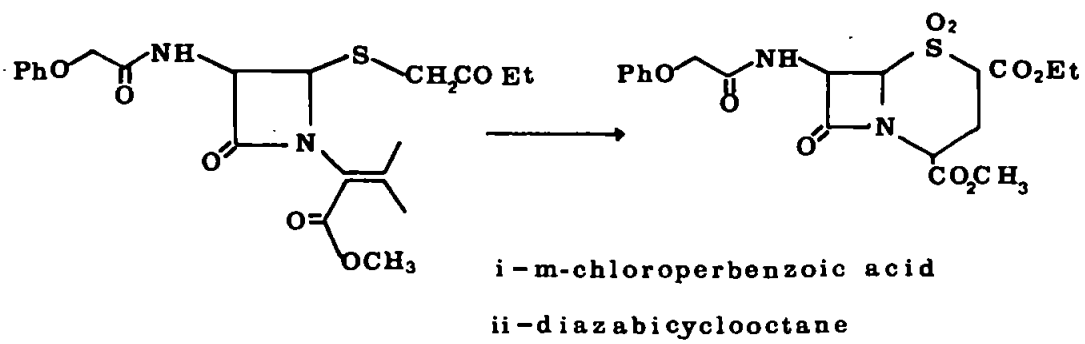
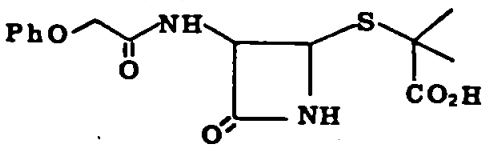
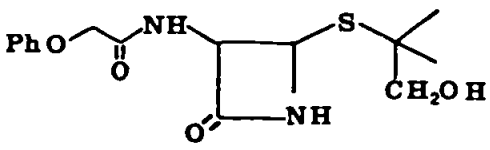


Fig 4·2

Since a range of S-substituents may be introduced by the alkylative cleavage and the N-substituent subsequently replaced, seco penicillins provide a possible route to derivatives which are not directly available via 3-4 cleavage. Compounds derived from 3-4 cleavage necessarily have sulphur carrying the residual carbon skeleton of the thiazolidine ring, for example 6 and 7, - Sheehan and Brondt, 1965 [53] and Heusler and Woodward, 1970 [54] respectively.



6.

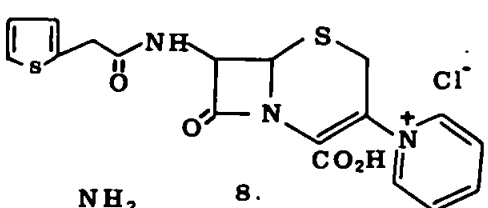


7.

The extensive chemistry of monocyclic β- lactams has been reviewed by Mukerjee and Singh, 1975 [55].

4.3 Structure Activity Relationships

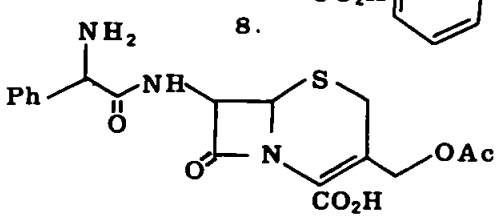
In the previous chapter, mention was made of the apparent link between antibiotic activity and lactom C-N bond cleavage susceptibility in fused ring compounds. The mechanism of cleavage, and factors which are thought to determine the stability of the β lactam system, have been discussed by Sweet and Dahl (ref 32a) and subsequently by Sweet (ref 32b). Sweet and Dahl compared the molecular parameters of the active compounds cephaloridine, 8 and cephaloglycine, 9 with those of the inactive phenoxymethyl Δ^2- desacetoxyl cephalosporin 10 and noted that N_5 in active compounds was significantly more pyramidal than in inactive compounds.



8.

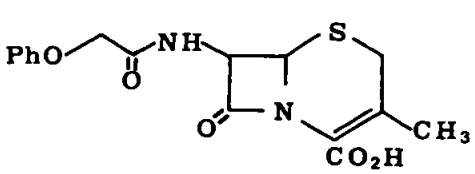
N_5 - to plane
Å

0·24



9.

0·22



10.

0·065

It was also found that in active compounds the lactam C-N was longer and the C-O shorter than the corresponding exocyclic amide bonds. In contrast, these distances for both the lactam and exocyclic amide of 10 were close to those in a normal amide, and N_5 was only very slightly out of the plane of its substituent atoms. The increased N-C distance and higher C=O stretching frequency of active compounds indicated a reduced degree of amide resonance stabilization, Fig 4.3, also section 3.7, Fig 3.8, Sweet and Dahl suggested that in active compounds, loss of this stabilization facilitates formation of a tetrahedral intermediate at C7(8) during nucleophilic attack.

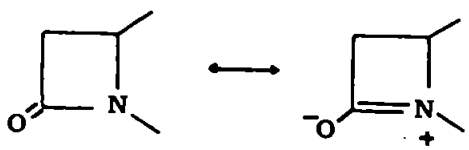


Fig 4·3

The steric requirements in Δ^2- cephalosporins dictate non planarity of the nitrogen and in cephaloridine, bond lengths provide evidence that enamine resonance, Fig 4.4 causes partial delocalization of the lone pair into the Δ^2 bond, with consequent reduction in the contribution to amide resonance.

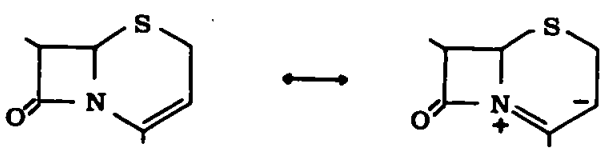
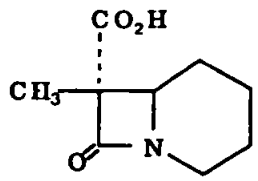
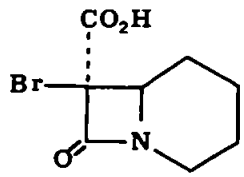


Fig 4·4

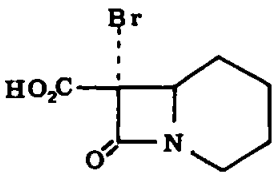
The planarity of the bridgehead nitrogen atom in inactive β- lactams was examined by Bender and Rapoport, 1975 [56], who determined the crystal structures of the aza-bicyclo (4.2.0) - octanes 11-13. Deviations from planarity were very small, although two were slightly greater than that reported by Vijayan et al, 1973 [57] for the inactive compound 14.



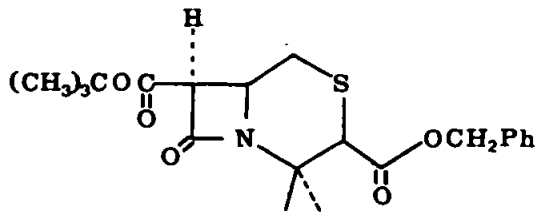
11. $\Delta = -0.121$ Å



12. $\Delta = -0.143$ Å

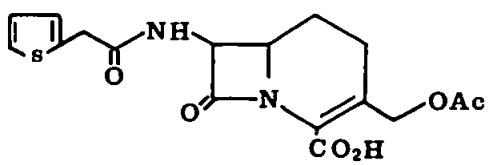


13. $\Delta = -0.089$ Å

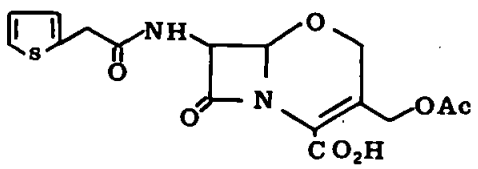


14. $\Delta = -0.100$ Å

Unlike the very active carbacephalothin 15, Guthikonda, 1974 [58], none of the compounds 10-14 have a Δ-3 double bond which could participate in enamine resonance. The high potency of both 15, and the oxacephalothin analogue 16 prepared by Cama and Christensen 1974 [59], was thought to result from increased ring strain, caused by replacement of sulphur with a smaller atom.

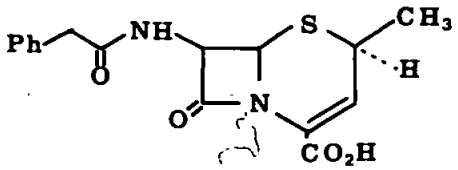


15.

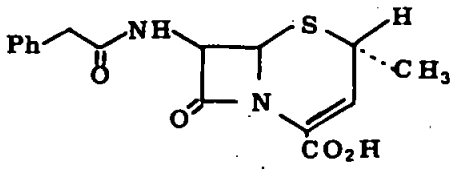


16.

From the activity shown by 15 and 16 and the 2-methyl-3-cephem epimers 17 and 18 recently reported by Kamiya et al, 1976 [60], it is apparent that neither the atomic species at position 1 nor the state of substitution at position 2 are as important as the presence of the Δ3 double bond in determining activity in cephalosporin analogues.



17.



18.

Epimer 17 was found to be almost as active as natural desacetoxyl cephalosporin, while 18 was more active. In view of the preceeding discussion, the seco penicillin was expected to show only a small deviation from planarity, of the ring nitrogen from its bonded atoms. Bond lengths were thus expected to reflect a degree of lactam amide resonance consistent with the observed planarity.

Experimental

4.4 Crystal Preparation

The crystals used in this work were the acicular prisms illustrated in Plate (2), Fig 1.2a,section 1.5, obtained by recrystallisation of the seco penicillin from acetone-water. The compound showed no apparent deterioration during exposure in the X-ray beam.

4.5 Space Group and Unit Cell Determination

Preliminary photographs showed the seco penicillin to crystallise in the monoclinic system. Mirror symmetry about a plane normal to the rotation axis was evident in an oscillation photograph, and the absence of symmetry about the non orthogonal axes in a Weissenberg photograph of a crystal rotated about its long axis, confirmed this to be the unique b-axis. Systematic absences $0k0 = 2n + 1$ evident in a Weissenberg photograph of a crystal rotated about the a-axis indicated space group $P2_1$ or $P2_1/m$. The presence in the molecule of an asymmetric centre however, excludes centrosymmetric space groups, and the compound was therefore assigned to space group $P2_1$. The density determined by

flotation in potassium iodide solution was found to be 1,251 kg/m^3 the calculated value being 1,244 kg/m^3 for Z = 2 molecules per unit cell.

Unit cell parameters were determined as in 2.3 from gold wire calibrated Weissenberg photographs. Least squares refinement of $2\theta_{hkl}$ for ten h0l and eleven 0kl reflections yielded the following values with e.s.d's in parentheses with respect to the last significant figures.

$$a = 9.389\ (19)\text{Å}$$

$$b = 11.411\ (5)\ \text{Å}$$

$$c = 15.019\ (7)\ \text{Å}$$

$$\beta = 98.599\ (62)^\circ$$

4.6 Data Collection and Preliminary Treatment

Multifilm data was collected using the Nonius Weissenberg camera and CuK_α radiation by the equi-inclination method. Data was collected about the b axis for the ten levels h0l -h9l using exposure periods of 4 days. Additional data was collected for each level using 2 hour exposures, in order to bring the most intense reflections within measurable ranges. The crystal was measured with the aid of a graticule and found to have dimensions 0.60 x 0.15 x 0.13 mm.

Weissenberg film measurements were carried out at the S.R.C. Microdensitometer Service, Chilton. Of the 2945 accessible reflections, 2632 were of measurable intensity and 313 were classed as unobserved. Intensity data were subjected to Lp corrections and converted into Fobs. values by the HKLF and MERG sections of the SHEL-X programme. The estimated overall isotropic temperature factor derived by this programme was U = 0.058.

4.7 Structure Determination

The presence of a sulphur atom in the molecule enabled the structure to be solved by the heavy atom method. For space group $P2_1$ with equivalent positions x, y, z, $\bar{x}$, y + $\frac{1}{2}$, $\bar{z}$, for a pair of atoms at these positions has coordinates 2x, $\frac{1}{2}$, 2z on the v = $\frac{1}{2}$ section.

The v = $\frac{1}{2}$ section of the three dimensional Patterson map illustrated in Fig 4.5, revealed two large peaks P_A and P_B, either of which could have been due to the sulphur-sulphur vector. The alternative sulphur coordinates in the direct cell were therefore derived as follows:

	u	v	w		x	y	z
P_A	0.552	0.500	0.658	S_A	0.276	0.500	0.329
P_B	0.434	0.500	0.815	S_B	0.217	0.500	0.407

Two Fourier syntheses were then computed using F_o as coefficients and phases based on the alternative sulphur positions. In an effort to determine which sulphur atom position was the correct one, the highest peaks in these Fourier syntheses were assumed to correspond to atomic positions and the vectors relating these positions to the sulphur atom were calculated and compared with those present in the Patterson map. Only one of the first twelve vectors calculated from the Fourier map phased on S_A coincided with peaks on the Patterson map but nine of those calculated from the Fourier map phased on S_B coincided in this way. The sulphur position S_B was therefore selected as the correct one.

The Fourier synthesis phased on S_B contains an artificial mirror plane in the y plane containing the sulphur atom. In order to eliminate the extra atomic positions indicated by the presence of this artificial symmetry, the phasing process must be carried out very carefully (section 2.12). In the first Fourier refinement, the light atom peak at x = 0.410, y = 0.115, z = 0.262, thought to be N_1 was given the scattering factor for nitrogen and included with the sulphur atom in a Fourier

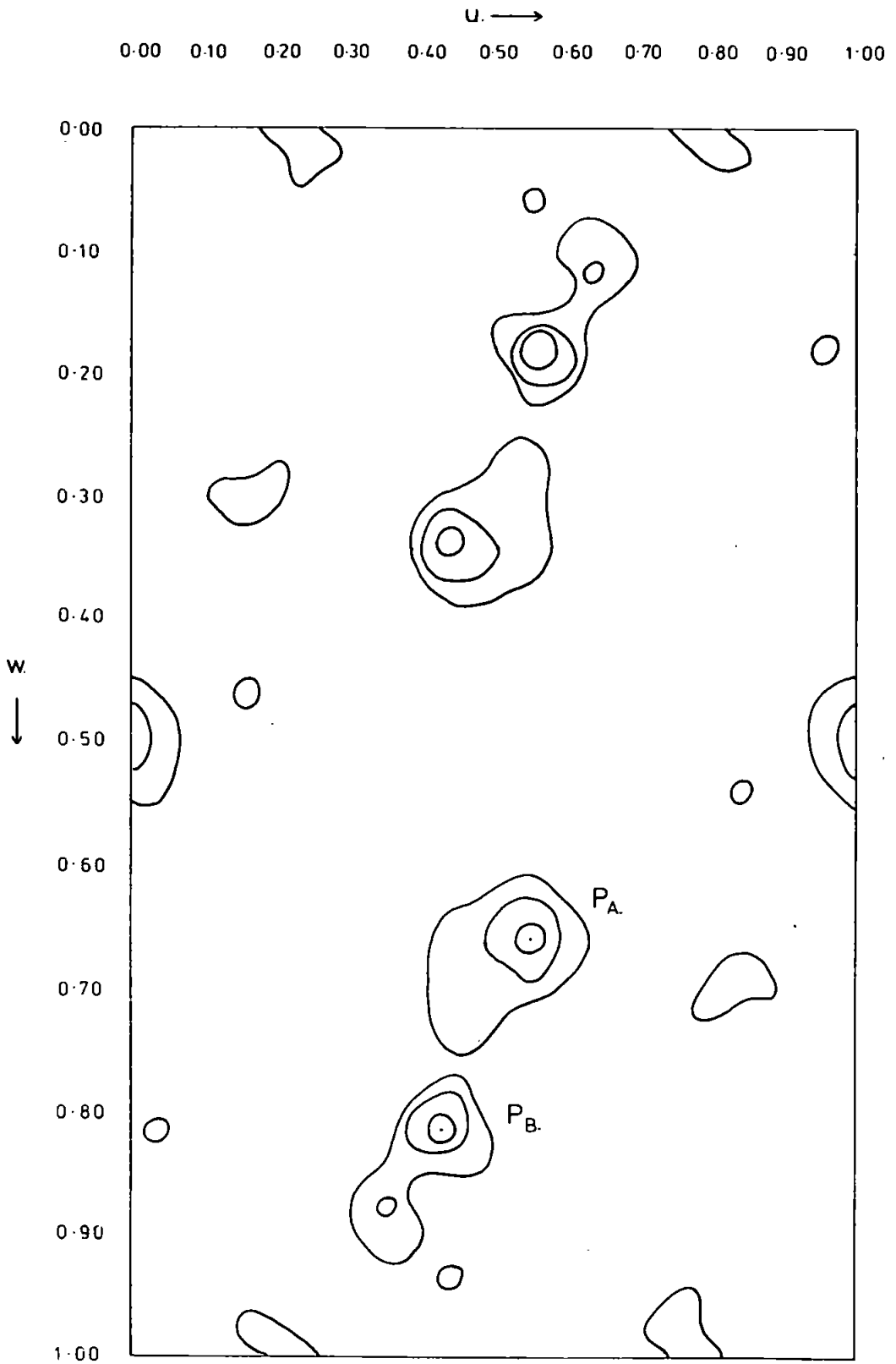


Fig 4·5 - Patterson section v = 1/2 for seco-penicillin, EB 976.

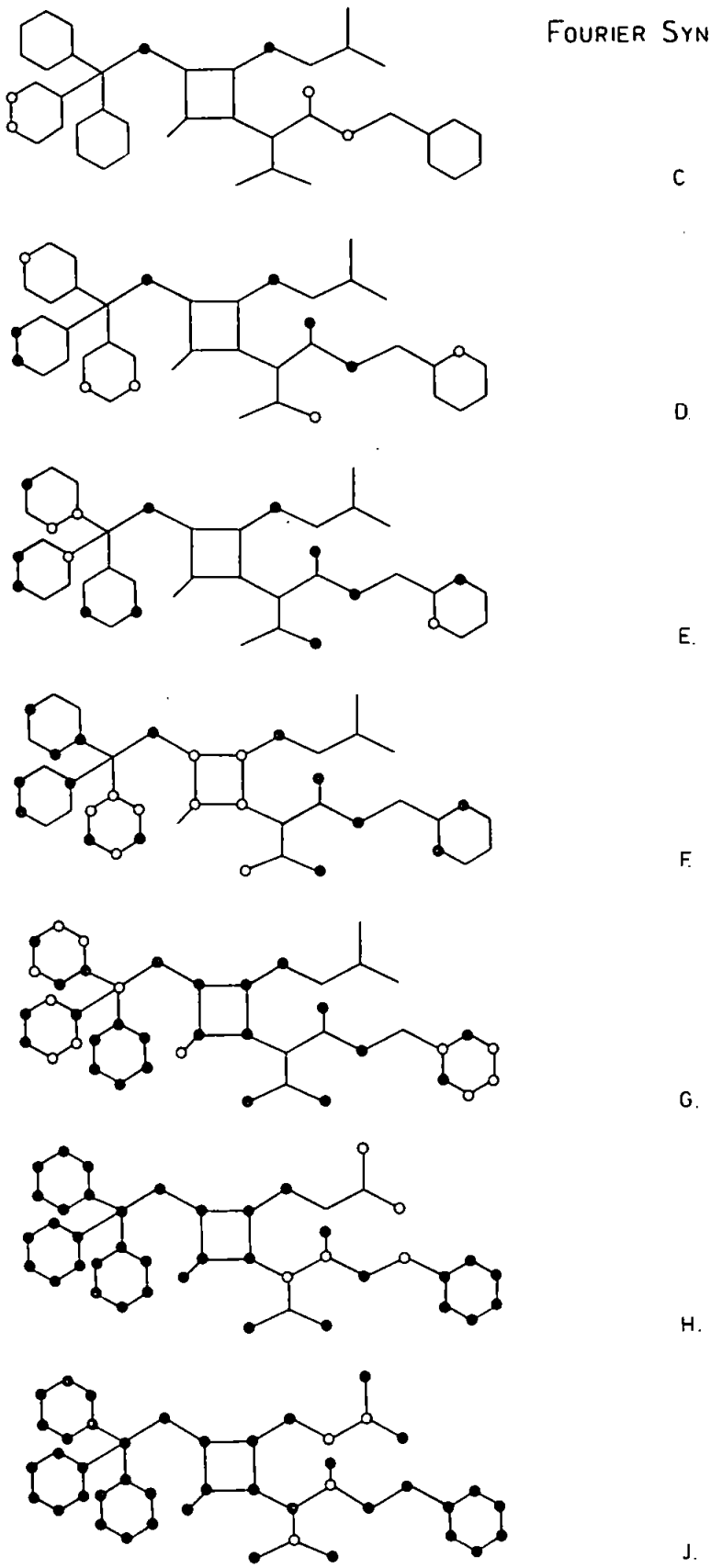


Fig 4·6 Progress of the structure determination of the seco-penicillin, EB 976.

synthesis, "C". The output map revealed a number of peaks with intensities biased towards one or other side of the $y = \frac{1}{2}$ section, and six of these were selected for addition to the phasing model for synthesis "D". Two of these subsequently proved to be spurious but the other four and N_1 correctly represented atomic positions, shown in C of Fig 4.6, which illustrates the progress of the structure determination. The atomic positions used to phase the reflections in the Fourier synthesis, are represented by shaded circles and those determined from the synthesis are drawn as open circles.

The identification of particular atoms only became possible after a further three syntheses, when the lactam ring and one benzene ring were recognized - Fig 4.6 F. Progress thereafter was accelerated with location of the remaining aromatic carbon atoms in the following syntheses, Fig 4.6 G, and completion of the non hydrogen skeleton in the next two, Fig 4.6 H, J. Interlayer scale factors, positional and thermal parameters were refined in the latter stages but the unweighted R factor did not fall below 0.146 until hydrogen atoms had been included and further refinement carried out as described in 3.6.

4.8 Refinement of the Structure

Aromatic carbon atoms were fitted to regular hexagons, with intercarbon distances fixed at 1.395Å, for isotropic rigid group refinement. Hydrogen atoms were assumed to be at their calculated positions, which were in agreement with a difference map, with the exception of one terminal H-atom of the methyl-allyl group.

The remaining non aromatic skeletal atoms were refined anisotropically, the molecule being partitioned into four sections, Fig 4.7 to keep the number of simultaneously refined parameters within the programme limit of 265. These sections were then refined in pairs, to provide overlap as indicated in Fig 4.7.

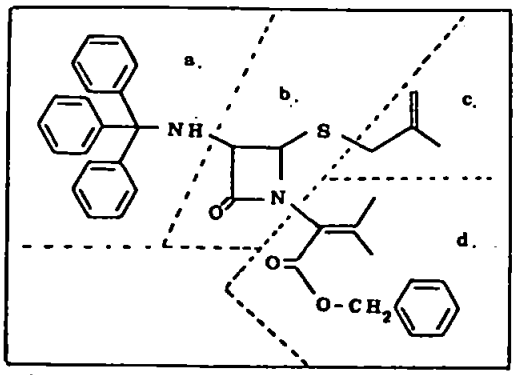


Fig 4.7 Sectioning for SHEL-X 'BLOC' refinement.

Cycle	Sections Refined	
1	a	d
2	b	c
3	a	b
4	c	d

Interlayer Scale factors were refined and U_{22} was constrained to be equal to the mean of U_{11} and U_{33} the data having been collected along the b-axis.

The final value of the unweighted R factor for the refined structure was 0.0768. Structure factors for the seco penicillin are listed in Appendix C.

4.9 Discussion of the Structure

Final positional and thermal parameters are listed in Tables VIII and IX. Bond lengths and angles are listed in Tables X and XI and are illustrated in Figs 4.8 and 4.9.

The crystal structure, as viewed from the +a direction, normal to the plane of the page, is illustrated in Fig 4.10 in which the largest shaded circles represent atoms closest to the viewer. In the interest of clarity, hydrogen atoms have not been included in Fig 4.10.

The overall shape of the molecule is apparent in Fig 4.10, which shows the expected cis configuration of the trityl-amino and alkyl-thio

TABLE VIII

Positional and thermal parameters for the non-hydrogen atoms of E.B. 976, obtained from least squares refinement.

- Positional parameters are given as fractions of cell edges x 10^4.
- Isotropic temperature factors are of the form exp $(-B \sin^2 \theta/\lambda^2)$.
- Anisotropic temperature factors are expressed as -

$$\exp\left[-2\pi^2 (U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*\right]$$

The units of B are Å^2 x 10^2 and those of U_{ij} are Å^2 x 10^4. Standard deviations in parentheses are with respect to the last figure (s) given.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	4207(5)	1619(5)	2703(3)	399(21)	369(11)	340(20)	-33(18)	-26(18)	-47(18)
C2	3939(6)	0529(5)	2161(3)	363(23)	344(12)	325(22)	-45(19)	27(19)	27(19)
C3	4958(4)	9558(3)	2631(3)	361(11)					
C4	6132(4)	9869(3)	3270(3)	423(25)					
C5	7077(4)	9008(3)	3664(3)	531(15)					
C6	6848(4)	7836(3)	3419(3)	584(17)					
C7	5674(4)	7525(3)	2780(3)	526(14)					
C8	4729(4)	8386(3)	2386(3)	490(15)					
C9	2339(4)	177(4)	2107(2)	337(10)					
C10	1317(4)	635(4)	1426(2)	389(12)					
C11	9856(4)	413(4)	1426(2)	486(14)					
C12	9417(4)	9733(4)	2107(2)	483(14)					
C13	438(4)	9275(4)	2788(2)	520(13)					
C14	1899(4)	9497(4)	2788(2)	439(13)					

Continued .....

TABLE VIII (continued)

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C15	4430(4)	694(3)	1235(2)	357(11)					
C16	3955(4)	9919(3)	535(2)	417(12)					
C17	4484(4)	9(3)	282(2)	488(14)					
C18	5488(4)	875(3)	400(2)	513(15)					
C19	5963(4)	1650(3)	300(2)	534(15)					
C20	5434(4)	1560(3)	1117(2)	446(13)					
C21	727(4)	6801(4)	1153(3)	522(15)					
C22	479(4)	7109(4)	763(3)	455(31)					
C23	354(4)	7936(4)	72(3)	575(39)					
C24	9024(4)	8455(4)	9770(3)	694(44)					
C25	7819(4)	8147(4)	161(3)	519(34)					
C26	7943(4)	7320(4)	852(3)	558(16)					
C27	9315(4)	5921(10)	1880(7)	576(43)					
O28	760(6)	5521(6)	2242(4)	635(29)	701(15)	763(30)	-72(26)	18(26)	269(25)
C29	9206(6)	3923(9)	4483(7)	713(46)	802(26)	891(54)	-172(48)	269(43)	17(43)
C30	8316(11)	2929(11)	3057(9)	598(47)	938(32)	1275(74)	-210(65)	-29(54)	35(45)
C31	9207(8)	2944(7)	3801(6)	452(32)	613(19)	774(41)	-57(34)	185(32)	-93(28)
C32	296(8)	1999(7)	4009(6)	479(33)	615(19)	755(41)	-24(35)	195(32)	-96(30)
S33	2156(2)	2500(0)	4066(1)	488(7)	472(5)	436(6)	17(6)	89(5)	36(6)
C34	2157(6)	3105(6)	2950(4)	354(24)	374(12)	394(24)	-41(22)	33(21)	22(22)
C35	3329(6)	2624(6)	2392(3)	416(23)	372(12)	329(22)	20(22)	66(20)	52(24)
C36	4022(6)	3839(6)	2554(4)	408(25)	377(13)	349(24)	-5(21)	70(21)	46(22)

Continued .....

TABLE VIII (continued)

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C37	5082(5)	4328(5)	2370(3)	545(23)	540(12)	538(23)	-15(20)	201(20)	-69(20)
N38	2942(5)	4233(5)	2987(3)	393(21)	410(12)	431(22)	-85(20)	78(19)	67(19)
C39	2666(6)	5299(6)	3420(4)	445(26)	414(13)	387(24)	14(22)	95(22)	94(24)
C40	1249(7)	5842(7)	3096(5)	512(30)	517(16)	525(30)	72(28)	133(27)	30(28)
O41	597(6)	6473(6)	3531(4)	713(32)	764(17)	818(33)	-154(29)	234(27)	343(28)
S42	3467(10)	6923(8)	4524(5)	854(46)	693(22)	536(37)	149(34)	143(37)	111(42)
C43	3622(7)	5752(6)	4081(4)	573(31)	486(15)	401(26)	2(25)	149(25)	65(27)
C44	4964(8)	5106(7)	4429(5)	632(37)	589(18)	546(34)	-33(30)	11(31)	-1(32)

TABLE IX

Coordinates of hydrogen atoms of E.B. 976 given as fractions of cell edges x 10^4 with estimated standard deviations in parentheses with respect to the last figures quoted.

Atom	x	y	z
H N1	5015(5)	1661(5)	3295(3)
H C4	6309(4)	776(3)	3460(3)
H C5	7986(4)	9242(3)	4159(3)
H C6	7580(4)	7170(3)	3724(3)
H C7	5496(4)	6618(3)	2591(3)
H C8	3819(4)	8156(3)	1892(3)
H C10	1658(4)	1162(4)	898(2)
H C11	9066(4)	768(4)	899(2)
H C12	8286(4)	9562(4)	2107(2)
H C13	98(4)	8748(4)	3316(2)
H C14	2690(4)	9142(4)	3316(2)
H C16	3178(4)	9248(3)	626(2)
H C17	416(4)	9408(3)	9176(2)
H C18	5898(4)	944(3)	8968(2)
H C19	6741(4)	2320(3)	209(2)
H C20	5802(4)	2160(3)	1659(2)
H C22	1508(4)	6707(4)	996(3)
H C23	1287(4)	8174(4)	9769(3)
H C24	8927(4)	9095(4)	9235(3)
H C25	6789(4)	8549(4)	9928(3)
H C26	7010(4)	7082(4)	1154(3)
H C27(1)	8689(9)	5171(10)	1614(7)
H C27(2)	8837(9)	6301(10)	2423(7)

Continued..

TABLE IX (continued)

Atom	x	y	z
H C29(1)	24(10)	3761(9)	5055(7)
H C29(2)	8164(10)	3969(9)	4703(7)
H C29(3)	9428(10)	4743(9)	4171(7)
H C30(1)	8330(100)	2367(48)	2731(63)
H C32(1)	172(8)	1613(7)	4649(6)
H C32(2)	95(8)	1343(7)	3487(6)
H C34	1028(6)	2992(6)	2694(4)
H C35	3025(6)	2230(6)	1738(3)
H C42(1)	2465(10)	7327(8)	4231(5)
H C42(2)	4355(10)	7483(8)	4420(5)
H C42(3)	3470(10)	6799(8)	5237(5)
H C44(1)	5590(8)	5612(7)	4956(5)
H C44(2)	5585(8)	4968(7)	3888(5)
H C44(3)	4693(8)	4269(7)	4695(5)

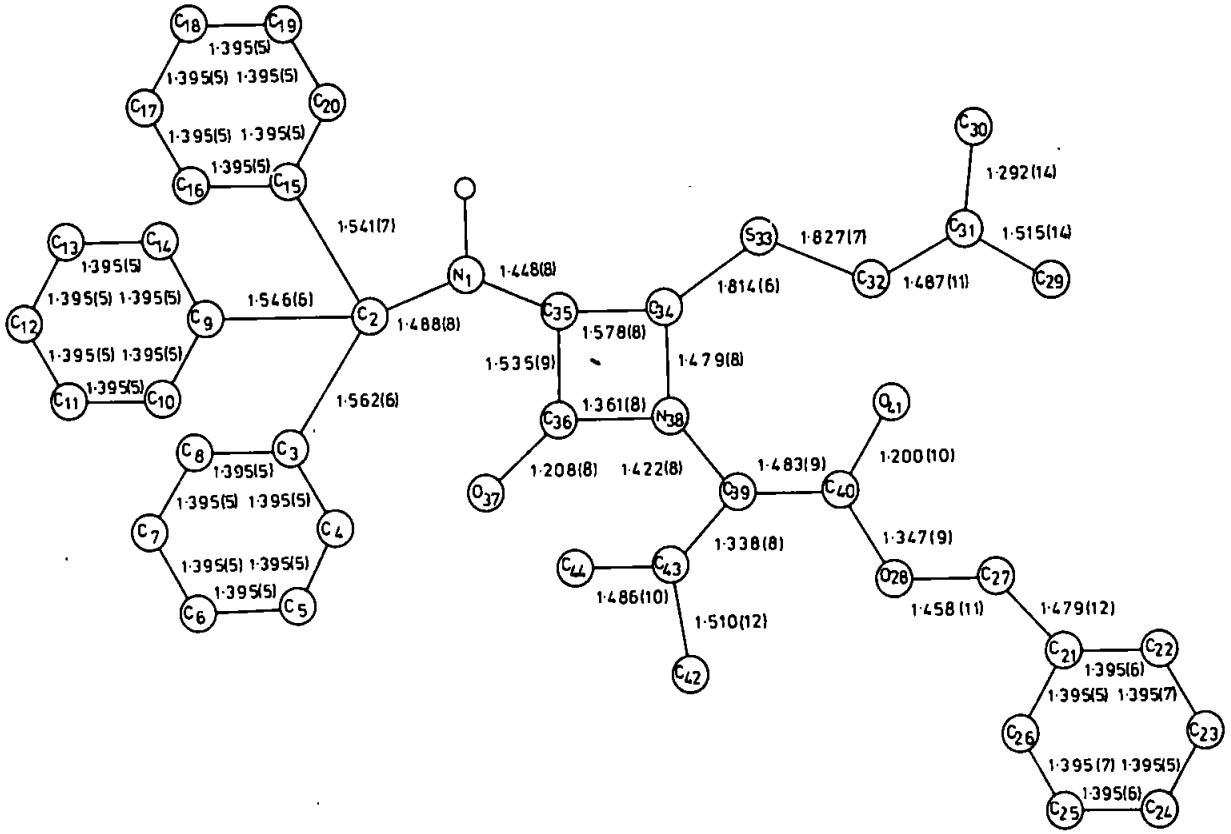


Fig 4·8 – Bond distances for the seco-penicillin E.B. 976 (Å)

TABLE X

Bond distances for E.B. 976 in Å with e.s.d's in parentheses with respect to the last figures quoted. Phenyl groups (C_3 - C_8), (C_9 - C_{14}), (C_{15} - C_{20}) and (C_{21} - C_{26}) were refined isotropically as rigid hexagons with intercarbon distances fixed at 1.395Å.

Bond A - B	Distance Å
N1 - C2	1.488(8)
C3 - C2	1.562(6)
C9 - C2	1.546(6)
C15 - C2	1.541(7)
N1 - C35	1.448(8)
C34 - C35	1.578(8)
C36 - C35	1.535(9)
C36 - O37	1.208(8)
C34 - N38	1.479(8)
C36 - N38	1.361(8)
C39 - N38	1.422(8)
C39 - C43	1.338(8)
C42 - C43	1.510(12)
C44 - C43	1.486(10)
C39 - C40	1.483(9)
O41 - C40	1.200(10)
O28 - C40	1.347(9)
O20 - C27	1.458(11)
C21 - C27	1.479(12)
C29 - C31	1.515(14)
C30 - C31	1.292(14)
C32 - C31	1.487(11)
C32 - S33	1.827(7)
C34 - S33	1.814(6)

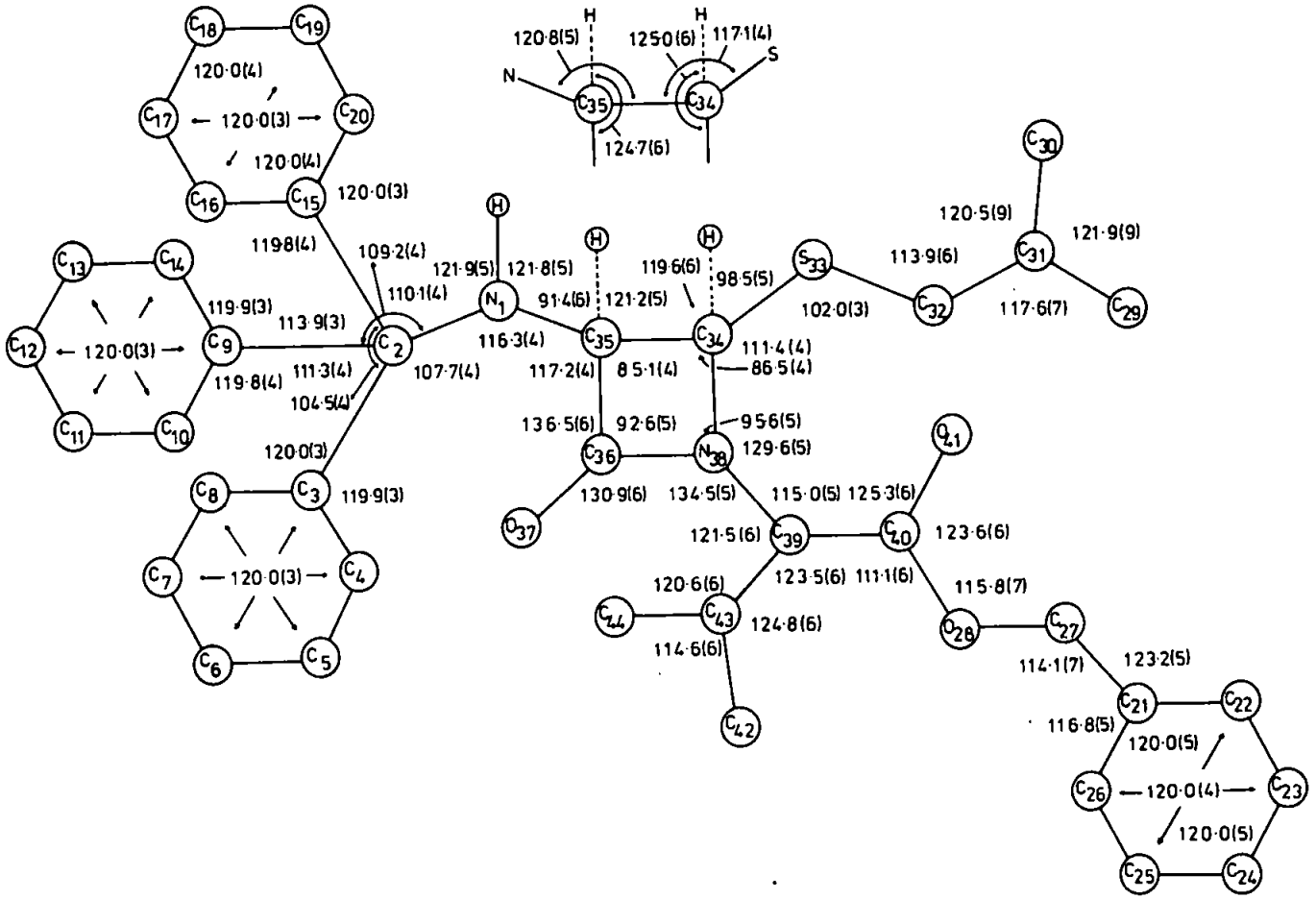


Fig 4·9 - Bond angles for the seco-penicillin, EB 976.

(degrees)

TABLE XI

Bond angles for E.B. 976, in degrees with estimated standard deviations in parentheses, with respect to the last figures(s) quoted. (Phenyl rings, R_1 - (C_3 - C_8), R_2 - (C_9 - C_{14}), R_3 - (C_{15} - C_{20}) and R_4 - (C_{21} - C_{26}) were refined as rigid hexagons).

Angle A-B-C	Degrees	Angle A-B-C	Degrees
C3 C2 N1	107.7(4)	C10 C9 C2	119.8(4)
C9 C2 N1	109.2(4)	C14 C9 C2	119.9(3)
C9 C2 C3	111.3(4)	C15 C16 C17	120.0(3)
C15 C2 N1	110.1(4)	C16 C17 C18	120.0(3)
C15 C2 C3	104.5(4)	C17 C18 C19	120.0(4)
C15 C2 C9	113.9(3)	C18 C19 C20	120.0(3)
H1 N1 C2	121.9(5)	C19 C20 C15	120.0(3)
C35 N1 C2	116.3(4)	C20 C15 C16	120.0(4)
C35 N1 H1	121.8(5)	C16 C15 C2	119.8(4)
C3 C4 C5		C20 C15 C2	120.0(3)
C4 C5 C6		C32 S33 C34	102.0(3)
C5 C6 C7		O37 C36 N38	92.6(5)
C6 C7 C8	120.0(3)	C35 C36 O37	136.5(6)
C7 C8 C3		C34 N38 C36	95.6(5)
C8 C3 C4		C39 N38 C36	134.5(5)
C4 C3 C2	119.9(3)	C3 N38 C34	129.6(5)
C8 C3 C2	120.0(3)	N38 C34 S33	111.4(4)
C9 C10 C11		H34 C34 S33	98.5(5)
C10 C11 C12		H34 C34 N38	125.0(6)
C11 C12 C13		C35 C34 S33	117.1(4)
C12 C13 C14	120.0(3)	C35 C34 N38	86.5(4)
C13 C14 C9		C35 C34 H34	119.6(6)
C14 C9 C10			

Continued .....

TABLE XI (continued)

Angle A-B-C	Degrees	Angle A-B-C	Degrees
C36 C35 N1	117.2(4)	028 C40 041	123.6(6)
C34 C35 N1	120.8(5)	C27 028 C40	115.8(7)
C34 C35 C36	85.1(4)	C21 C22 C23	120.0(4)
H35 C35 N1	91.4(6)	C22 C23 C24	120.0(4)
H35 C35 C36	124.7(6)	C23 C24 C25	120.0(5)
H35 C35 C34	121.2(5)	C24 C25 C26	120.0(4)
C30 C31 C29	121.9(4)	C25 C26 C21	120.0(4)
C32 C31 C29	117.6(7)	C26 C21 C22	120.0(5)
C32 C31 C30	120.5(9)	C27 C21 C22	123.2(5)
C31 C32 S33	113.9(6)	C27 C21 C26	116.8(5)
C40 C39 N38	115.0(5)	C21 C27 028	114.1(7)
C43 C39 N38	121.5(6)	C44 C43 C39	120.6(6)
C43 C39 C40	123.5(6)	C42 C43 C39	124.8(6)
041 C40 C39	125.3(6)	C42 C43 C44	114.6(6)
028 C40 C39	111.1(6)		

R_4

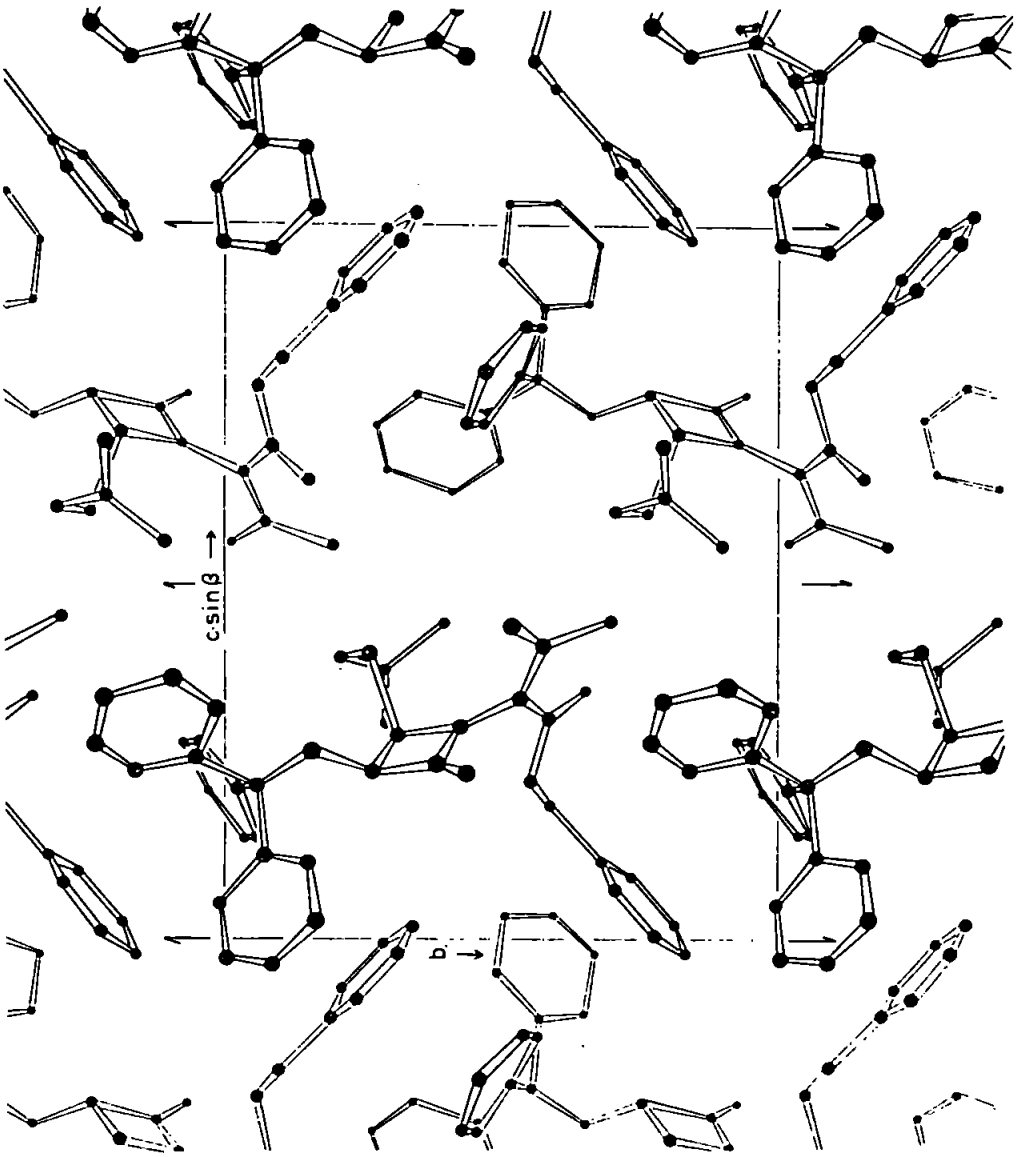


Fig 4·10 – Structure of the seco penicillin EB 976 as viewed from the direction of +a.

substituents. In the following discussion the primary feature of interest is the β- lactam ring, the detailed geometry of which is compared with that of several important fused ring compounds.

Compounds b - d in Fig 4.11 are among those which have been subjected to detailed comparison by Sweet in reference [32b], and their particular relevance is as follows:

(b) 3 benzyl 7-t-butyl 2, 2, - dimethyl - 8 - oxo - 4 thia - 1 - aza - 6αH - bicyclo [4·2·0] octane - 3β, 7α - dicarboxylate - Vijayan et al 1973 [57].

(Sweet's abbreviation syn-ceph will be used herein). Syn-ceph has near-planar bridgehead nitrogen bonding geometry, as a result of reduced ring strain relative to Δ-3 cephalosporins or penicillins, and has no antibiotic activity.

(c) Anhydro - α - phenoxyethyl penicillin, Wolfe et al, 1968 [61].

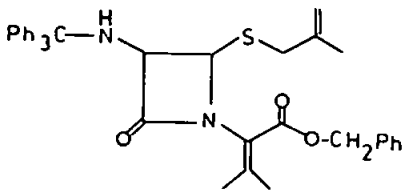
(Sweet's abbreviation an-pen will be used herein).

Although an-pen has a similar degree of pyramidal character of N_4 bonding to that in active penicillins, it is stable to basic hydrolysis conditions, and is inactive. Sweet regarded the absence of activity as somewhat anomalous, although Wolfe, who first prepared anhydropenicillins, considered that the absence of a carboxyl function would preclude activity. An-pen is included in this discussion because the unsaturated system adjacent to N_4 is closely similar to that in the corresponding region of the seco penicillin.

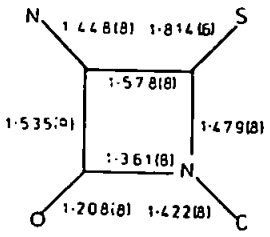
(d) 6 β- amino penicillanic acid - Diamond 1963 [40]. (abbreviated to 6 APA).

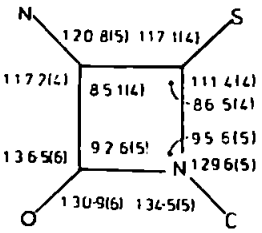
Since a large number of active penicillins have been derived by acylation of this intermediate, the β- lactam ring parameters of 6 APA are included in Fig 4.11 for comparison purposes, as being representative of active penicillins.

COMPOUND	BOND LENGTHS	BOND ANGLES

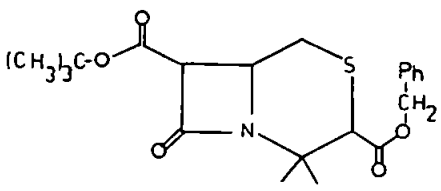


a.- Title Compound

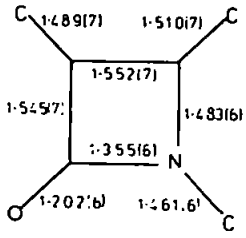


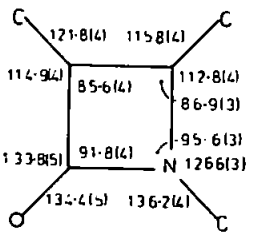


$\Delta_{(N\text{-}Plane)} = 0{\cdot}04$ Å

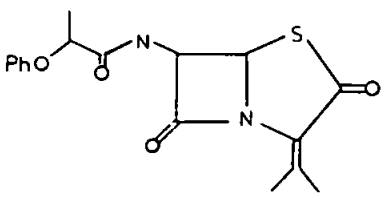


b.- Syn-Ceph.

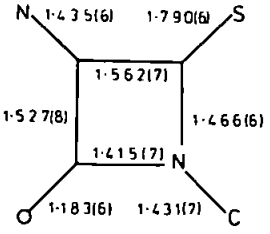


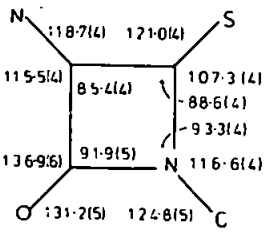


$\Delta_{(N\text{-}Plane)} = 0{\cdot}10$ Å

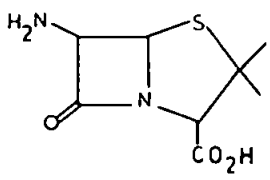


c.- An-Pen.

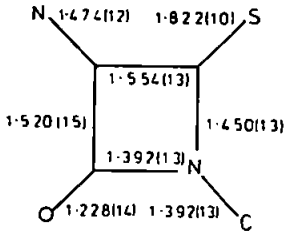


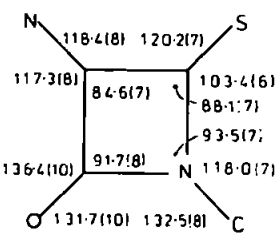


$\Delta_{(N\text{-}Plane)} = 0{\cdot}42$ Å



d -6-APA





$\Delta_{(N\text{-}Plane)} = 0{\cdot}32$ Å

Fig 4·11 – Comparison of β-lactam parameters.

It is instructive to consider individual bond lengths and angles in order to assess the degree of resonance stabilization in the seco penicillin, relative to that in b - d.

A. Bond Lengths

(i) The C-N bond:

At 1.361(8)Å this is close to the value of 1.355(6)Å for syn-ceph, but somewhat less than that for 6 APA, 1.392(13)Å, an-pen, 1.415(7)Å or penicillin V, 1.46(2)Å. The C-N distance for unstrained lactams, quoted by Sweet, is 1.347(7)Å.

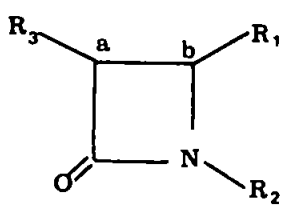
(ii) The C=O bond:

While the value 1.208(8)Å is close to that of syn-ceph, 1.206(6)Å, it has been noted by Sweet that carbonyl bond length differences are barely significant, although a systematic small decrease is apparent with increasing pyramidal character of the bridgehead nitrogen in fused ring β- lactams.

(iii) The exocyclic N-C bond:

The bond length 1.422(8)Å is close to the corresponding C_3-N_4 distance of 1.431(7)Å in an-pen, reflecting the almost identical electronic environment of the bonded $^{S}P_2$ hybridised carbon. In syn-ceph this distance is slightly greater, at 1.461(6)Å .

B. Bond Angles

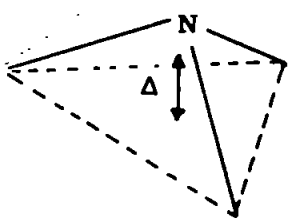


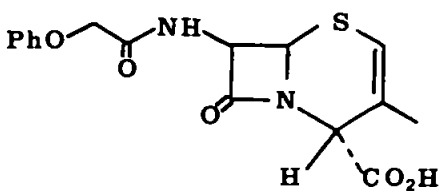
(i) External angles OCC_a, OCN and R_3C_aC for the seco penicillin are all closer to those of an-pen and 6 APA than to syn ceph. The remaining external angles are closer to those of syn ceph than to an-pen or 6 APA.

(ii) Internal angles CNC_b, C_aC_bN of the seco compound are also closer to syn-ceph angles than to those of an-pen, or 6 APA, while differences between compounds, for angles CC_aC_b and C_aC_bN, are less pronounced.

C. Deviation of N_{38} from the plane defined by its bonded atoms

The plane defined by C_{34} C_{36} and C_{39} is expressed in direct space by the equation $Px + Qy + Rz = S$ where $P = 3.886$, $Q = 3.448$, $R = 11.823$ and $S = 3.256$. The deviation of N_{38} from this plane is $\Delta = 0.045$Å, somewhat less than the corresponding distance in syn ceph, of 0.10Å, but close to the figure of 0.06Å for phenoxymethyl Δ^2 -desacetoxyl cephalosporin. (Sweet and Dahl 1970 ref [32a]) (abbreviated to 2-cephem).





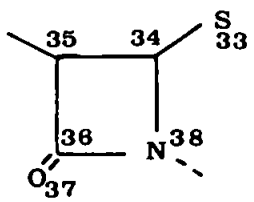
2-cephem

D. Deviation of O_{37} from the least squares plane of the lactam ring

The least squares plane defined by atoms C_{34} C_{35} C_{36} and N_{38} is expressed in direct space by the equation $Px + Qy + Rz = S$ where $P = 3.891$, $Q = 3.427$, $R = 11.828$ and $S = 3.245$.

The distances of the defining atoms from the plane are as follows:

C_{34}	0.020Å
C_{35}	-0.019Å
C_{36}	0.022Å
N_{38}	-0.023Å



The carbonyl oxygen, O_{37} is 0.055Å from the plane.

From Fig 4.11, it may be seen that the angles about C_a and C_b, and the external bond lengths, vary as expected, with the atomic species of

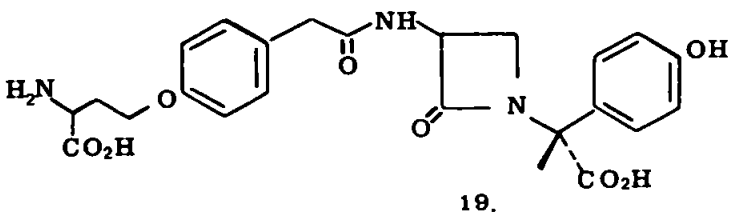
the substituent atom, and the size of the fused ring, in Fig 4.11 b, c, d and these parameters are not therefore comparable.

However, the structural parameters of the $>N - \underset{|}{C} = O$ system, in particular the N_{38}-C_{36} bond length, of the seco penicillin appear to be consistent with resonance stabilization of the same order as in syn-ceph.

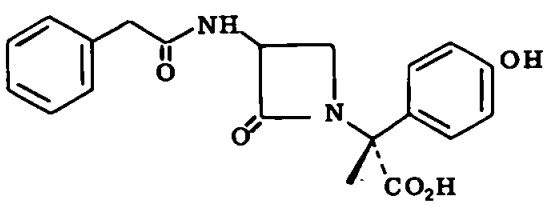
Conclusion

The similarities between the parameters of the seco penicillin and those of syn ceph reflect the unstrained bonding about the β- lactam nitrogen in these compounds. Although a degree of ring strain appears to be a necessary if not sufficient condition for activity in fused ring β- lactams, the essentially planar disposition of the lactam nitrogen and its substituent atoms in N-substituted monocyclic azetidin-2-ones does not preclude activity.

Since the activity of the nocardicins 5a, b was reported to be associated with some kind of inhibition of cell wall synthesis, their potency may prove to be due to a mode of action which is mechanistically analogous to that of penicillins. Should this be so, the presence of the oxime function in nocardicins, may be of secondary importance, in which case the analogues 19, 20 might also be active.



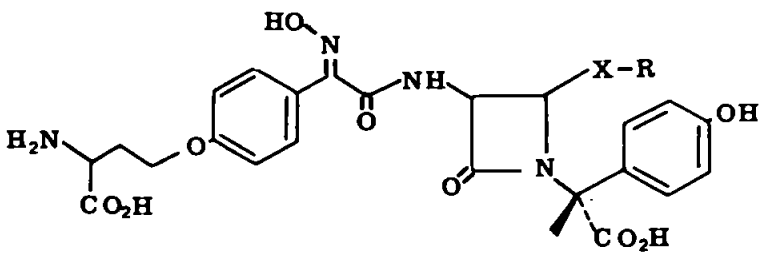
19.



20.

The detection of activity in these would be particularly significant as there would then be reason to postulate an inverse relationship between activity and electronegativity of the C_4 substituent in monocyclic β- lactams. Even if the oxime function is necessary for activity in nocardicins, evaluation of C_4 substituted analogues 21 would provide useful information. Should either 19 or 20 be active, the effects of C_4 substitution could be investigated in these, which might be more easily accessible.

The effects of various ring nitrogen substituents might be determined by evaluating compounds like 22.



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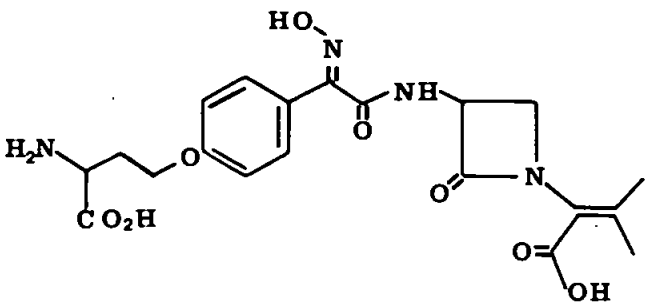
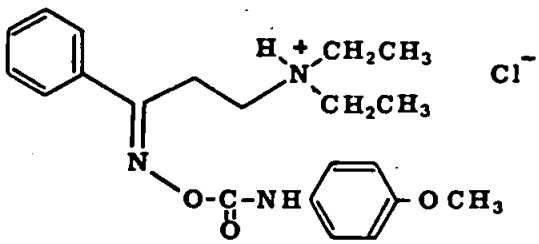


22.

The activity of the nocardicins may therefore be useful in determining structure activity relationships in the seco penicillin group.

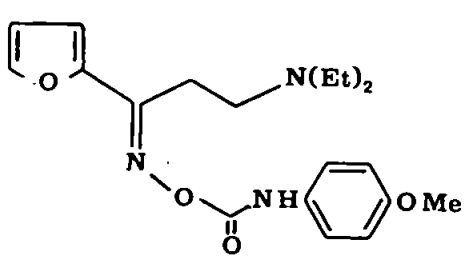
CHAPTER 5

The Crystal and Molecular Structure of Anidoxime - a Carbamoyl Oxime Ester



5.1 Introduction

Anidoxime, O-(4-methoxyphenylcarbamoyl)-3-diethylaminopropriophenone oxime hydrochloride, ($C_{21}H_{27}N_3O_3 \cdot HCl$), is a non narcotic analgesic approximately equipotent with morphine, and is one of a series of carbamoyl oxime esters described in British Patents 1,214,077 - (1970) and 1,295,115 - (1972). The range of substituents carried by the more active analogues, is illustrated by compounds (1) - (2) and (3) - (6) from the first and second of these patents respectively.



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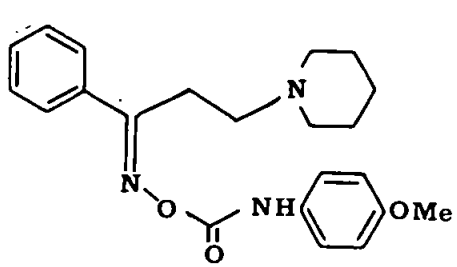

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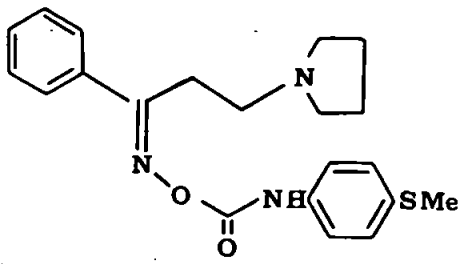

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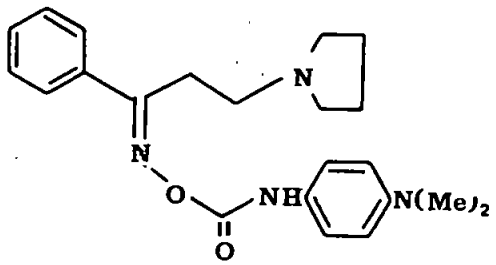

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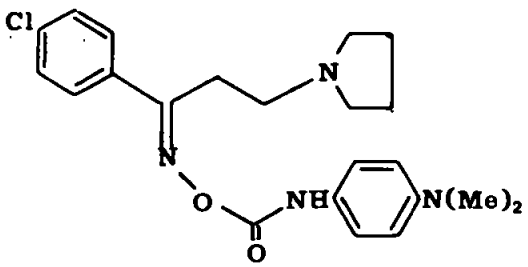

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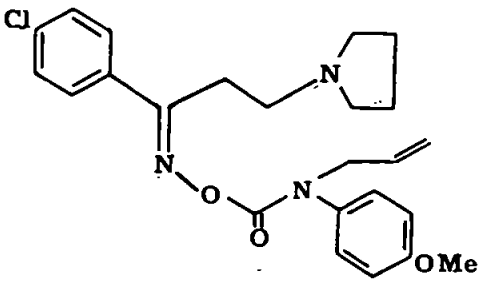
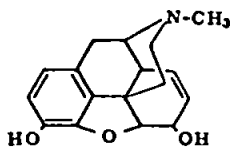


6.

This chapter describes the pharmacological interest of the carbamoyl oxime esters, and includes a short review of previous work on these compounds. Anidoxime has been selected as being representative of the series, for crystallographic structure investigation. Its crystallisation, structure determination and refinement are described in detail.

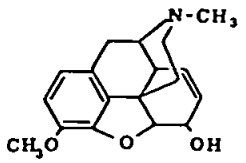
5.2 Chemical Significance of Anidoxime

The relationship between anidoxime and contemporary analgesics may be illustrated by comparison with the examples in Fig 5.1, drawn from

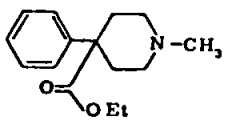


Morphine

MORPHINE GROUP

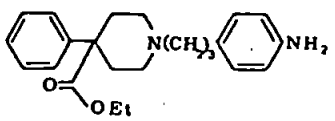


Codeine

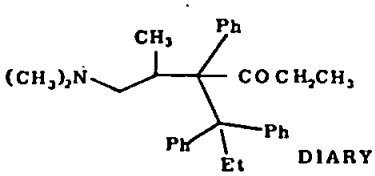


Meperidine

PHENYL PIPERIDINES

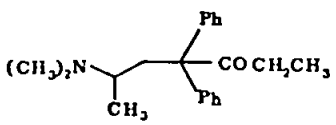


Anileridine

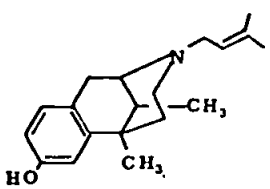


Dextropropoxyphene

DIARYLPROPYLAMINES

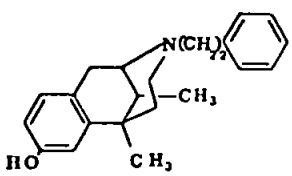


Methadone

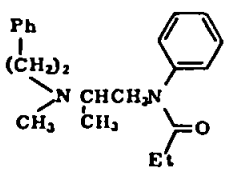


Pentazocine

BENZOMORPHANS

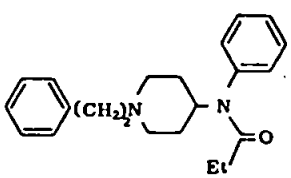


Phenazocine



Diampromid

BASIC ANILIDES



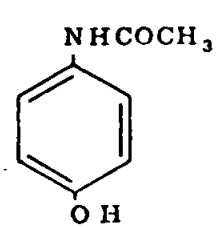
Fentanyl

Fig 5·1 - Contemporary analgesics.

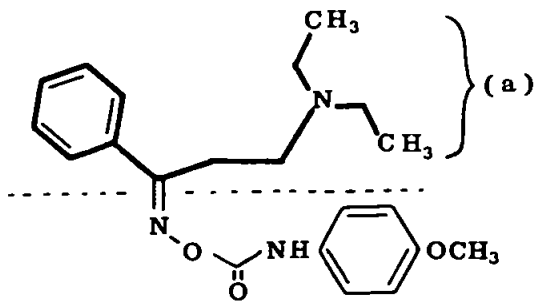
the principal groups in current use. Structure activity relationships of these and many other analgesics have been examined in detail in the comprehensive work of A.H. Beckett and A. F. Casy [62]. With few exceptions, analgesics, morphine - like or otherwise, contain a tertiary basic centre linked to a phenyl group by a three atom carbon chain, as illustrated in Fig 5.2. The chain may be part of a ring and the phenyl substituted atom is usually a quaternary carbon. If the chain contains either more or fewer than three carbon atoms, the potency is reduced except in the case of basic anilides, such as Diampromid, Fig 5.2d. These differ from diaryl-propylamines in that the quaternary carbon atom bearing two phenyl groups is replaced by a nitrogen atom bearing only one.

The high potency of some of these analgesics is thought to be partly dependent upon their ability to adopt optimum conformations at the receptor site. The importance of conformational factors was recently evaluated by Loew and Jester, 1975 [64] in their study relating the relative potency of (+) and (-) enantiomers of the α and β-prodines to the geometrical similarity of minimum energy conformers to morphine. The carbamoyl nitrogen of anidoxime and its analogues is usually mono substituted, $-\overset{O}{\overset{\|}{C}}-NH-R$ with optimum activity being observed when R = 4-alkoxy phenyl. There is a resemblance between the O substituent and simple anilide analgesics, i.e. phenacetin 7 and paracetamol 8.

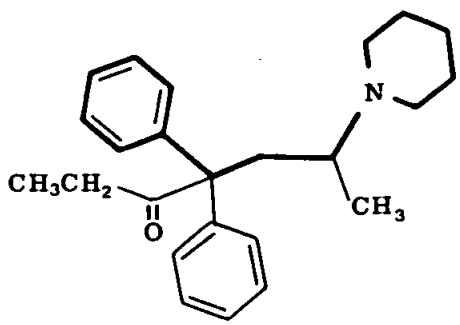
7.



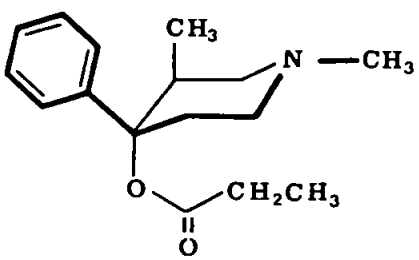
8.



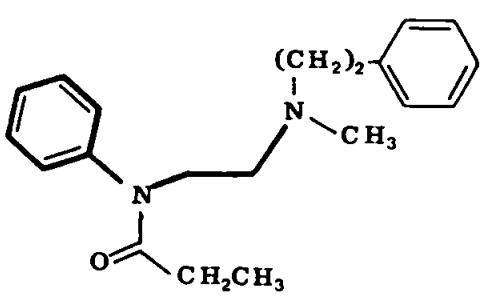
a.- Anidoxime



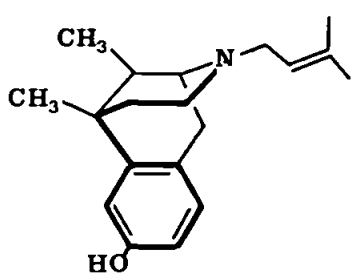
b.- Dipipanone



c.- ß-Prodine



d.- Diampromid



e.- Pentazocine

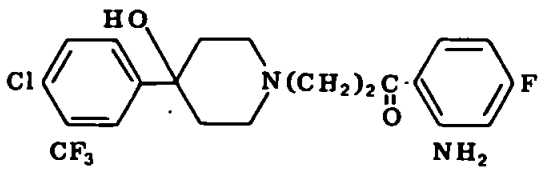
Fig 5·2- Activity related structural features.

The C=N-O-R entity appears to be the most unusual feature of the carbamoyl oxime group, and may be responsible for the non-morphine like nature of the activity. While established structure-activity relationships continue to provide a basis for development of improved piperidine and benzomorphon analgesics, [65 - 68], such as 9 and 10, there have been recent reports of activity among skeletally diverse[69-78] compounds, for example 11 - 16. Of these, 14 - 16 have the >C=N-O-R system as their only common structural feature.

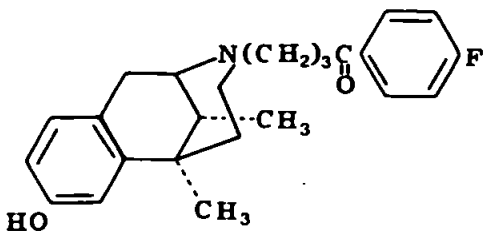
5.3 Pharmacological Significance of Anidoxine

The pharmacological evaluation of anidoxime has revealed it to be a non narcotic analgesic which differs from morphine and 4- phenyl piperidines particularly with respect to tolerance development and physical dependence liability. Tolerance development during prolonged use of analgesics seriously reduces the effectiveness of morphine like compounds. The increasing effective dose levels required, lead to greater manifestation of toxicity and side effects, and enhance the probability of physical dependence. Contemporary views on these topics and their interdependence are discussed in the comprehensive papers of J. Cochin, 1974 [79] and E. Leong Way 1974 [80].

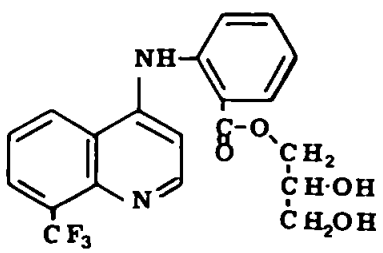
Extended quantitative studies of tolerance development have shown that anidoxime is 90% effective after 20 days by which time morphine is only 50% effective against a reproducible pain stimulus. The probability of physical dependence was reported to be negligible in tests with monkeys, and toxicity was acceptably low. The compound has however been shown to cause elevation of blood pressure and visual disturbances in an unacceptably large proportion of subjects during clinical trials.



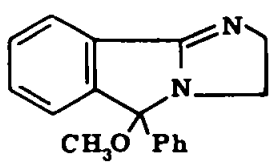
9.- ref.65



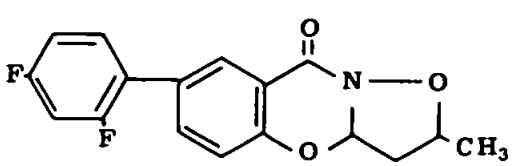
10.- ref. 68



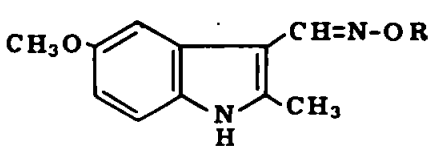
11.- ref. 69



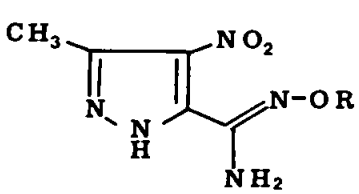
12.- ref. 70



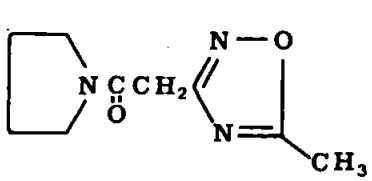
13.- ref. 73



14.- ref. 76



15.- ref. 77



16.- ref. 78

5.4 Crystal Preparation

The colourless transparent prisms obtained by crystallisation from water, as described in section 1.5 and illustrated in Fig 1.6 and Plate (7) were found to be of adequate size and satisfactory quality for data collection.

5.5 Space Group and Unit Cell Determination

The interaxial angles determined from Weissenberg photographs of crystals rotated about two orthogonal axial directions indicated that the crystals belong to the monoclinic system. The long axis of the crystals was found to be parallel to the crystallographic a-axis.

Systematic absences were observed in zero and upper level Weissenberg photographs, as follows:

	Class	Absences
Rotation axis a	0k0	k = 2n + 1
	001	l = 2n + 1
	101, 201, 301	l = 2n + 1
	hkl	no absences.
Rotation axis b	h0l	l = 2n + 1
	h1l	no absences.

These absences uniquely determined the space group to be $P2_1/c$.

Unit cell parameters were determined from Weissenberg photographs as described in 2.3, using gold wire for calibration. Least squares refinement of $2\theta_{hkl}$ for fourteen 0kl and six h0l reflections gave the following values, with e.s.d's in parentheses with respect to the last significant figures.

$$a = 7.366(55)\ \text{Å}$$

$$b = 17.537(35)\ \text{Å}$$

$$c = 16.481(12)\ \text{Å}$$

$$\beta = 101.18^{\circ}(25)$$

5.6 Data Collection and Preliminary Treatment

Multifilm data was collected using the Stoe camera, and Ni-filtered CuK_{α} radiation, by the equi-inclination method. Data was collected about the a - axis for the seven levels, 0kl - 6kl, using exposure periods of 96 hours for 5-film packs, and 90 minutes for the 3-film packs required to bring the most intense reflections within measurable range. A new crystal was used for each level, as deterioration of crystals became apparent after 180 hours in the X-ray beam.

Film intensity measurements were carried out at Chilton, at the Science Research Council Microdensitometer Service. Intensities were recorded for 2078 reflections, and these were subjected to Lp corrections and converted into E values by the HKLF and MERG sections of the SHEL-X programme.

5.7 Structure Determination and Refinement

The structure of anidoxime was solved, using the SHEL-X-"EEES" automatic centrosymmetric direct methods programme, which employs multisolution procedures.

The programme automatically selected three linearly independent origin defining reflections of high E, as follows:

h k l	E
$\bar{6}$ 4 1	4.10
$\bar{1}$ 5 2	2.65
0 9 1	1.58

These reflections were assigned + signs, and twelve other high E reflections were selected for generation of 2^{12} phase permutations.

SIGN EXPANSION PATHWAY FOR 11870

	H	K	L	E	SIGN RELATIONS															
1	-6	4	1	4.099	ORIG +															
2	-1	5	2	2.647	ORIG +															
3	0	9	1	1.576	ORIG +															
4	5	5	6	5.987	MULT+-															
5	5	7	1	2.785	MULT+-															
6	0	1	5	1.672	MULT+-															
7	-5	2	4	5.090	MULT+-															
8	1	4	3	1.856	MULT+-															
9	5	5	4	5.266	MULT+-															
10	-1	4	1	2.041	MULT+-															
11	-5	4	9	2.354	MULT+-															
12	0	4	5	1.490	MULT+-															
13	-6	4	3	2.509	MULT+-															
14	-4	4	5	2.680	MULT+-															
15	-5	4	5	5.021	MULT+-															
16	5	1	1	5.174	2• 1	4• 12	6• 7													
17	6	5	4	5.850	-6• 1	8• 16	-8• 5													
18	-6	2	1	2.973	-2• 5	-6• 17	-7• 8													
19	-6	0	6	5.077	-15• 10	-12• 1	11• 8													
20	-5	5	4	5.959	-19• 2	-15• 3	12• 16	11• 6												
21	0	2	5	1.629	-4• 5	-19• 18	-20• 5	11• 7												
22	0	5	10	1.384	4• 7	19• 17	11• 16	-11• 5	21• 6	12• 6										
23	-1	1	7	1.319	-4• 1	19• 16	-9• 13	-12• 2	22• 8											
24	-6	1	11	2.133	-11• 2	-22• 1	19• 6	-22• 18	23• 7											
25	-6	5	6	2.447	7• 2	6• 1	6• 18	-24• 21	-24• 12											
26	-5	8	4	2.212	8• 1	-25• 2	-22• 4	6• 5	-11• 12											
27	5	9	1	2.445	-2• 1	-4• 12	-12• 20	6• 26												
28	6	5	0	5.682	-16• 10	3• 1	27• 10													
29	-1	2	2	1.446	4• 17	19• 7	25• 20	21• 8	23• 6											
30	5	4	1	2.160	4• 6	-6• 20	21• 7	-29• 18	-12• 26	-23• 25										
31	-1	7	7	1.616	4• 18	19• 5	25• 30	24• 26	21• 2	-22• 8										
32	0	9	5	1.374	-4• 30	7• 5	-11• 20	26• 16	20• 30	8• 2	31• 29									
33	-6	12	1	2.268	2• 5	-31• 4	-32• 17	-26• 8	25• 32											
34	-6	8	6	1.819	15• 10	12• 1	31• 16	-11• 8	23• 5	-12• 33	23• 27	24• 32								
35	0	12	5	1.209	4• 5	20• 5	-34• 1	-19• 33	11• 26	26• 30	-31• 2	22• 32								
36	4	1	3	2.294	4• 8	-2• 30	29• 16	23• 7	31• 26											
37	-4	5	2	1.554	-7• 2	8• 16	26• 2	-8• 5	20• 29	-11• 31	21• 36	12• 36	11• 43							
38	1	6	3	1.342	-7• 1	-17• 27	4• 36	26• 18	-6• 2	-37• 27	12• 29									
39	1	8	8	1.541	20• 17	-11• 1	4• 37	11• 33	-22• 2	12• 8	-35• 8	21• 38								
40	6	1	9	1.516	-4• 8	-21• 17	-12• 17	22• 1	-4• 38	39• 5	22• 18	39• 27								
41	-5	5	14	2.505	22• 7	24• 8	11• 6	-39• 25	-11• 32	-22• 26	24• 38									
42	6	0	4	1.605	4• 2	12• 1	21• 18	-8• 30	39• 26	22• 25	35• 33	40• 6								
43	-6	9	11	1.756	11• 2	31• 7	-41• 8	19• 32	-22• 33	34• 6	-25• 35	23• 20								
44	-6	10	6	1.834	20• 2	-21• 33	-35• 18	23• 27	26• 29	-11• 38	43• 6	24• 32								
45	5	11	6	1.948	-31• 1	12• 5	21• 27	35• 16	22• 26	-23• 33	-39• 37									
46	-1	11	2	1.283	5• 1	27• 18	33• 16	25• 26	-26• 37	45• 42	-31• 12	22• 39	-23• 35							
47	5	10	1	2.377	-31• 25	35• 7	21• 26	-29• 33	45• 6	-36• 46										
48	0	8	4	1.751	-17• 28	-11• 15	8• 10	6• 3												
49	-5	13	10	5.174	41• 48	32• 15	11• 3	-43• 10												
50	0	3	6	1.436	15• 16	-19• 5	-36• 28	31• 10	-23• 10	35• 3										

Fig 5.3— Sign expansion pathway for anidoxime.

The relationship

$$S_h = S \Sigma \left[E_{h'} . E_{h-h'} \right]$$

forms the basis of the sign expansion during which the number of surviving sign permutations is reduced by progressive absolute figure of merit tests (M-abs) - Germain 1971 [14b]. The number of surviving permutations is further reduced at the end of the expansion process by the qt test - Giacovazzo 1974 [81] which utilizes information from low E and unobserved reflections.

In the expansion for anidoxime, a section of which is illustrated in Fig 5.3 the programme derived signs for 339 reflections using 2986 relations, and all but eight of the 2^{12} permutations of multisolution phase signs were eliminated. The E maps corresponding to the four most probable of these eight permutations were printed in order of decreasing probability as determined from a reliability index based on M(abs) and qt tests.

Of these four E maps, the first three showed marked similarities which allowed recognition of 19 of the 28 non hydrogen atoms, as represented by shaded circles in Fig 5.4.

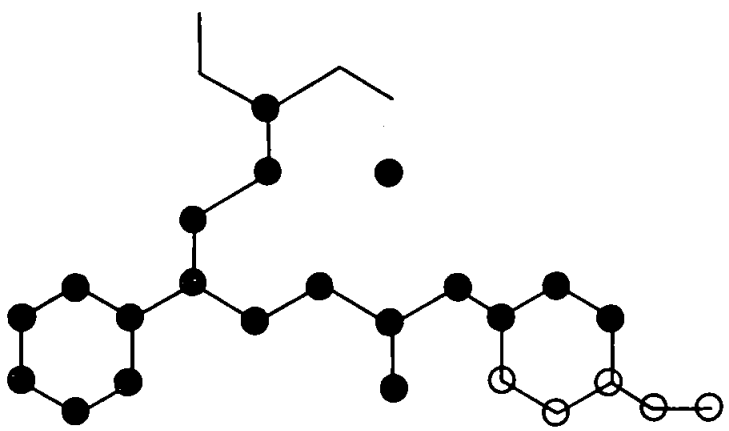


Fig 5·4

The positions of a further five atoms, drawn as open circles, were

also indicated, and although these were subsequently shown to be correct, they were not accepted at this stage.

The positional parameters of the first 19 atoms were subjected to four cycles of least squares refinement whereupon the unweighted R factor fell from 0.50 to 0.36. The locations of the remaining non-hydrogen atoms were clearly revealed in a difference synthesis, and when these were included in the model for a further synthesis, the value of R fell to 0.23. Three cycles of least squares refinement in which benzene rings were refined as rigid groups, lowered R to 0.14. A difference synthesis then revealed the positions of 26 of the 28 hydrogen atoms, and inclusion of these allowed refinement to R = 0.10, and identification of the remaining two H-atom locations.

All non-hydrogen atoms except aromatic carbons were then refined anisotropically with the value of R falling from 0.10 to 0.074 over two cycles. Finally, constraints were removed from the aromatic carbons, and two further cycles of least squares refinement gave a value R = 0.068.

Structure factors for anidoxime are listed in Appendix D.

5.8 Discussion of the Structure

Final positional and thermal parameters for anidoxime are listed in Tables XII and XIII. Bond lengths and angles are listed in Tables XIV and XV and are illustrated in Figs 5.5 and 5.6. A projection of the structure as viewed in the direction of the c-axis, is shown in Fig 5.7, which shows the arrangement of the cell contents. With the exception of H_9 and H_{23}, hydrogen atoms have been omitted from Fig 5.7 in the interest of clarity. The principal features of the structure are discussed below.

TABLE XII

Positional and thermal parameters for the non hydrogen atom of BRL 11870 obtained from least squares refinement with e.s.d's in parentheses with respect to the last figures given.

Positional parameters are given as fractions of cell edges x 10^4.

Isotropic temperature factors are of the form exp $(-B \sin^2\theta/\lambda^2)$.

Anisotropic temperature factors are expressed as:

$$\exp -2\pi^2 \left[U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*\right]$$

The units of B are Å^2 x 10^2 and those of U_{ij} are Å^2 x 10^4.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl	2821(2)	624(1)	4659(1)	537(5)	461(7)	580(9)	37(7)	29(5)	8(5)
C_1	640(6)	1175(3)	2247(3)	401(11)					
C2	9279(6)	839(3)	2604(4)	432(12)					
C3	7568(6)	663(3)	2121(4)	452(11)					
C4	7224(6)	834(3)	1290(4)	431(11)					
C5	8563(7)	1172(3)	930(4)	488(12)					
C6	248(6)	1344(3)	1405(4)	456(12)					
O7	5604(5)	676(3)	743(3)	548(11)	646(24)	458(23)	31(22)	1(17)	-58(17)
C8	4215(8)	288(4)	1072(4)	598(17)	703(37)	502(38)	-46(34)	132(28)	-93(27)
N9	2345(5)	1311(3)	2775(3)	442(11)	450(24)	434(25)	65(21)	45(18)	-82(16)
C10	3619(6)	1810(3)	2651(4)	440(13)	458(29)	422(32)	1(27)	10(22)	-50(19)
O11	3617(5)	2187(3)	2024(3)	608(12)	698(26)	522(26)	224(24)	-25(19)	-189(19)

Continued.....

TABLE XII (continued)

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O12	5059(4)	1748(2)	3295(3)	487(10)	496(22)	484(23)	114(19)	26(16)	-137(14)
N13	6429(5)	2306(3)	3268(3)	447(11)	431(23)	465(27)	35(22)	83(19)	-93(16)
C14	7793(6)	2175(3)	3853(3)	399(12)	345(24)	453(29)	-32(24)	115(21)	-19(18)
C15	9256(5)	2761(3)	3942(3)	368(10)					
C16	1071(7)	2582(4)	4278(4)	535(14)					
C17	2409(8)	3150(4)	4343(5)	642(16)					
C18	1939(8)	3876(4)	4104(5)	654(16)					
C19	137(8)	4051(4)	3776(4)	602(15)					
C20	8807(7)	3499(3)	3699(4)	505(13)					
C21	7929(6)	1522(3)	4447(3)	418(12)	369(25)	466(30)	18(24)	129(21)	-14(18)
C22	6919(6)	1741(3)	5145(3)	421(12)	430(27)	409(31)	33(24)	82(21)	5(18)
N23	7029(5)	1152(3)	5796(3)	403(11)	364(21)	441(25)	13(20)	79(18)	-48(15)
C24	8962(7)	975(4)	6229(4)	518(14)	457(31)	580(36)	95(30)	5(25)	26(21)
C25	73(8)	1653(4)	6574(5)	667(18)	686(42)	650(42)	74(39)	-115(30)	-194(29)
C26	5806(7)	1379(4)	6389(4)	554(16)	622(34)	487(36)	-1(31)	187(26)	-27(23)
C27	5347(10)	718(5)	6895(5)	752(21)	960(49)	541(43)	95(40)	228(32)	-169(35)

TABLE XIII

Positional parameters of the hydrogen atoms of BRL 11870, obtained from least squares refinement. Positional parameters are given as fractions of cell edges x 10^4.

Atom	x	y	z
H-C 2	9550(6)	715(3)	3259(4)
H-C 3	6616(6)	393(3)	2396(4)
H-C 5	8281(7)	1301(3)	277(4)
H-C 6	1289(6)	1613(3)	1122(4)
H-C8(1)	3013(8)	198(4)	586(4)
H-C8(2)	3808(8)	624(4)	1558(4)
H-C8(3)	4745(8)	9750(4)	1322(4)
H-N9	2577(5)	1080(3)	3313(3)
H-C16	1448(7)	2015(4)	4486(4)
H-C17	3840(8)	3014(4)	4587(5)
H-C18	2989(8)	4310(4)	4175(5)
H-C19	9764(8)	4622(4)	3577(4)
H-C20	7385(7)	3642(3)	3446(4)
H-C21(1)	7289(6)	1028(3)	4129(3)
H-C21(2)	9365(6)	1404(3)	4700(3)
H-C22(1)	5480(6)	1839(3)	4881(3)
H-C22(2)	7528(6)	2254(3)	5430(3)
H-N23	6537(5)	628(3)	5497(3)
H-C24(1)	8886(7)	594(4)	6734(4)
H-C24(2)	9670(7)	701(4)	5793(4)
H-C25(1)	1441(8)	1476(4)	6874(5)
H-C25(2)	9397(8)	1932(4)	7019(5)
H-C25(3)	181(8)	2039(4)	6077(5)

Continued....

TABLE XIII (continued)

Atom	x	y	z
H-C26(1)	6508(7)	1804(4)	6804(4)
H-C26(2)	4534(7)	1609(4)	6041(4)
H-C27(1)	4468(10)	906(5)	7311(5)
H-C27(2)	6609(10)	485(5)	7250(5)
H-C27(3)	4635(10)	290(5)	6487(5)

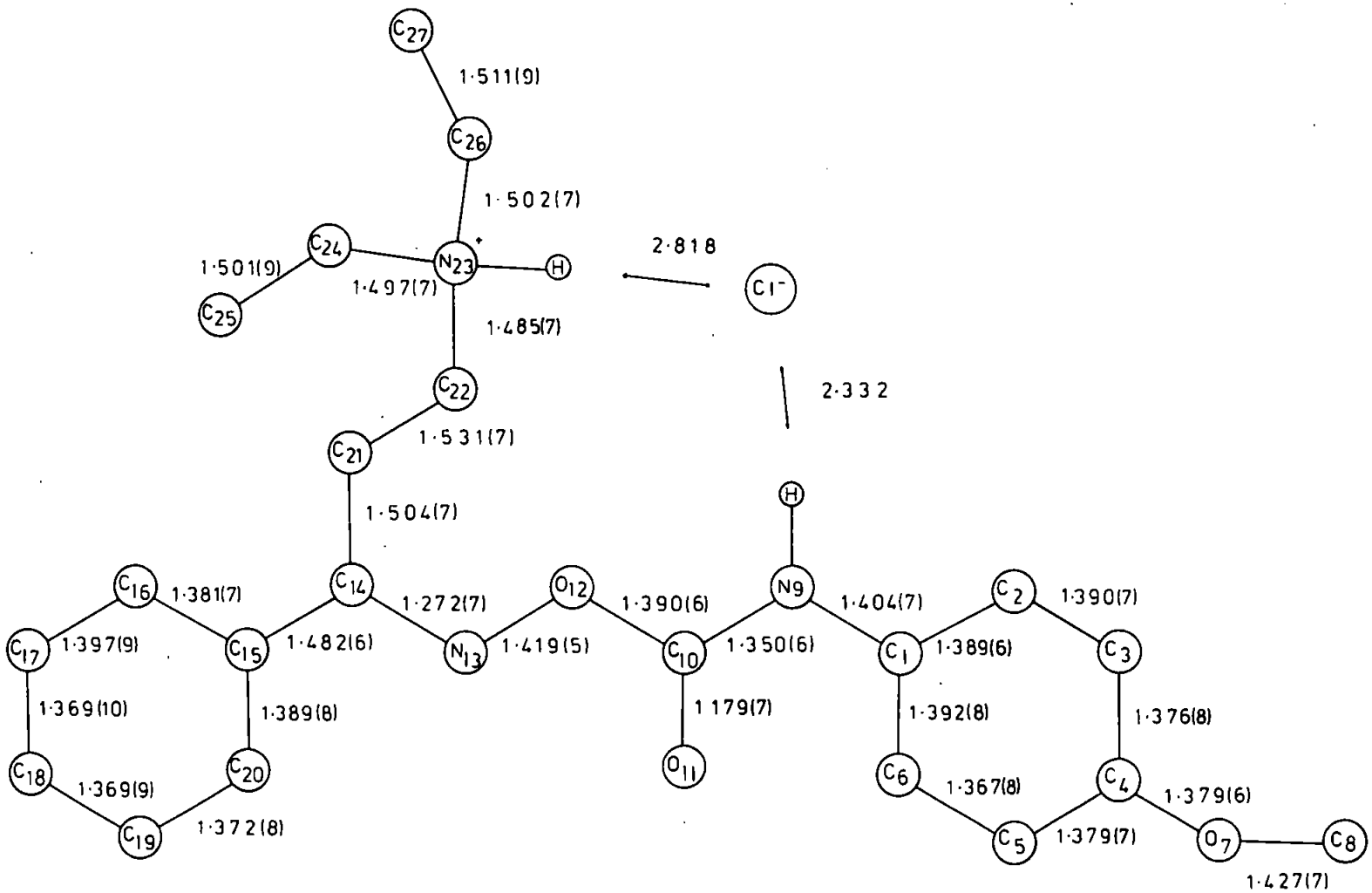


Fig 5·5 – Bond lengths for anidoxime, (Å)

TABLE XIV

Bond distances for ERL 11870 in Å with e.s.d's in parentheses with respect to the last figures given.

Bond A-B	Distance Å
C_1 - C2	1.389(6)
C2 - C3	1.390(7)
C3 - C4	1.376(8)
C4 - C5	1.379(7)
C5 - C6	1.367(8)
C4 - O7	1.379(6)
O7 - C8	1.427(7)
C1 - N9	1.404(7)
N9 - C10	1.350(6)
C10 - O11	1.179(7)
C10 - O12	1.390(6)
C12 - N13	1.419(5)
N13 - C14	1.272(7)
C14 - C15	1.482(6)
C15 - C16	1.381(7)
C16 - C17	1.397(9)
C17 - C18	1.369(10)
C18 - C19	1.369(9)
C19 - C20	1.372(8)
C20 - C15	1.389(8)
C14 - C21	1.504(7)
C21 - C22	1.531(7)
C22 - N23	1.485(7)
N23 - C24	1.497(7)
N23 - C26	1.502(7)
C24 - C25	1.501(9)
C26 - C27	1.511(9)

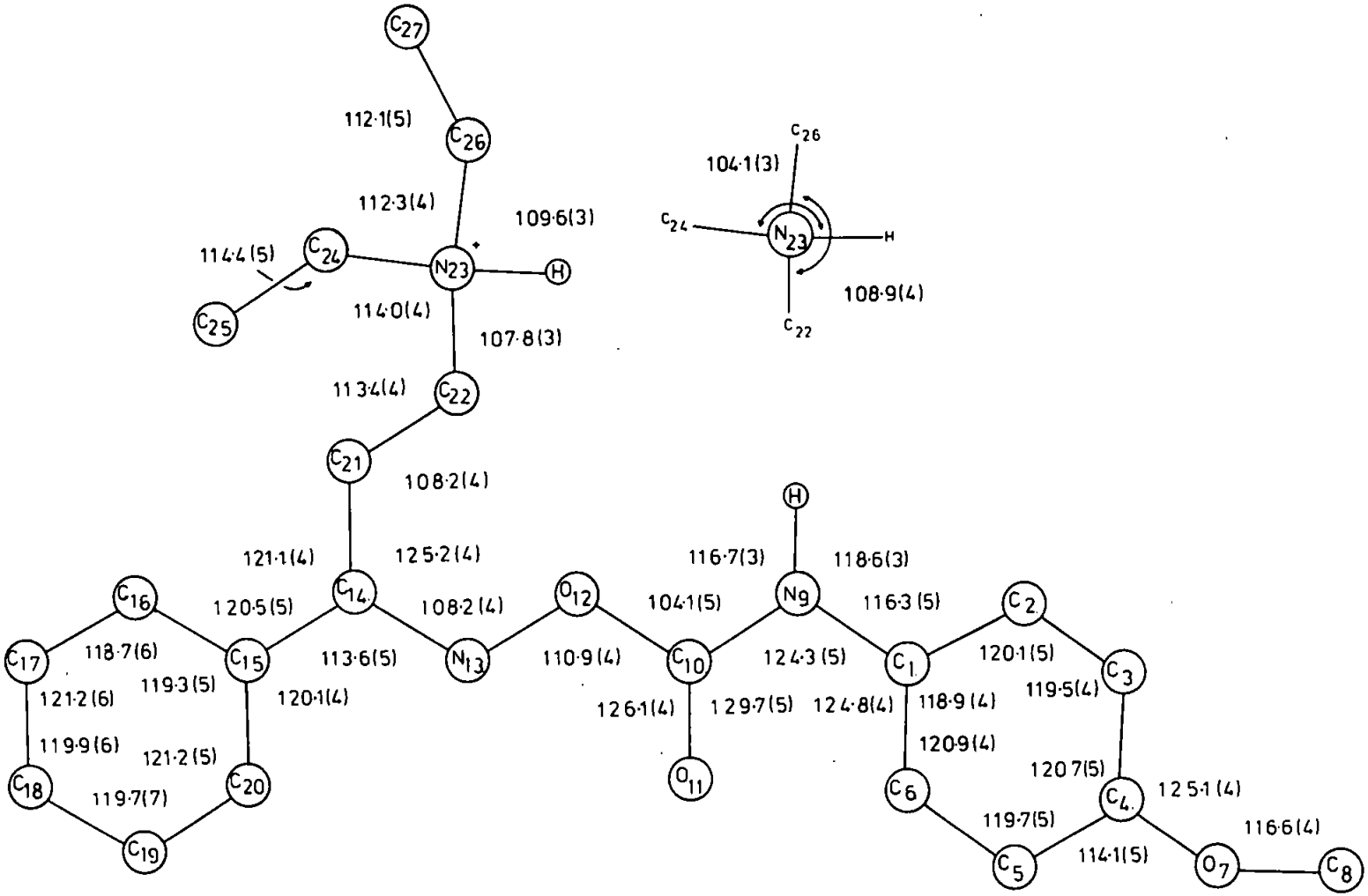


Fig 5·6 – Bond angles for anidoxime, (degrees)

TABLE XV

Bond angles for BRL 11870 in degrees with e.s.d's in parentheses with respect to the last figures given.

Angle ABC	Degrees	Angle ABC	Degrees
C_1 C2 C3	120.1(5)	N13 C14 C21	125.2(4)
C2 C3 C4	119.5(4)	C15 C14 C21	121.1(4)
C3 C4 C5	120.7(5)	C14 C15 C16	120.5(5)
C4 C5 C6	119.7(5)	C14 C15 C20	120.1(4)
C5 C6 C_1	120.9(4)	C15 C16 C17	118.7(6)
C6 C_1 C2	118.9(4)	C16 C17 C18	121.2(6)
C3 C4 O7	125.1(4)	C17 C18 C19	119.9(6)
C5 C4 O7	114.1(5)	C18 C19 C20	119.7(7)
C4 O7 C8	116.6(4)	C19 C20 C15	121.2(5)
C2 C_1 N9	116.3(5)	C20 C15 C16	119.3(5)
C6 C_1 N9	124.8(4)	C14 C21 C22	108.2(4)
C_1 N9 H9	118.6(3)	C21 C22 N23	113.4(4)
C10 N9 H9	116.7(3)	C22 N23 H23	107.8(3)
C10 N9 C_1	124.3(5)	C22 N23 C24	114.0(4)
N9 C10 O11	129.7(5)	C22 N23 C26	108.9(4)
N9 C10 O12	104.1(5)	H23 N23 C24	104.1(3)
O11 C10 O12	126.1(4)	N23 C24 C25	114.4(5)
N13 O12 C10	110.9(4)	N23 C26 C27	112.1(5)
C14 N13 O12	108.2(4)	C24 N23 C26	112.3(4)
N13 C14 C15	113.6(5)	H23 N23 C26	109.6(3)

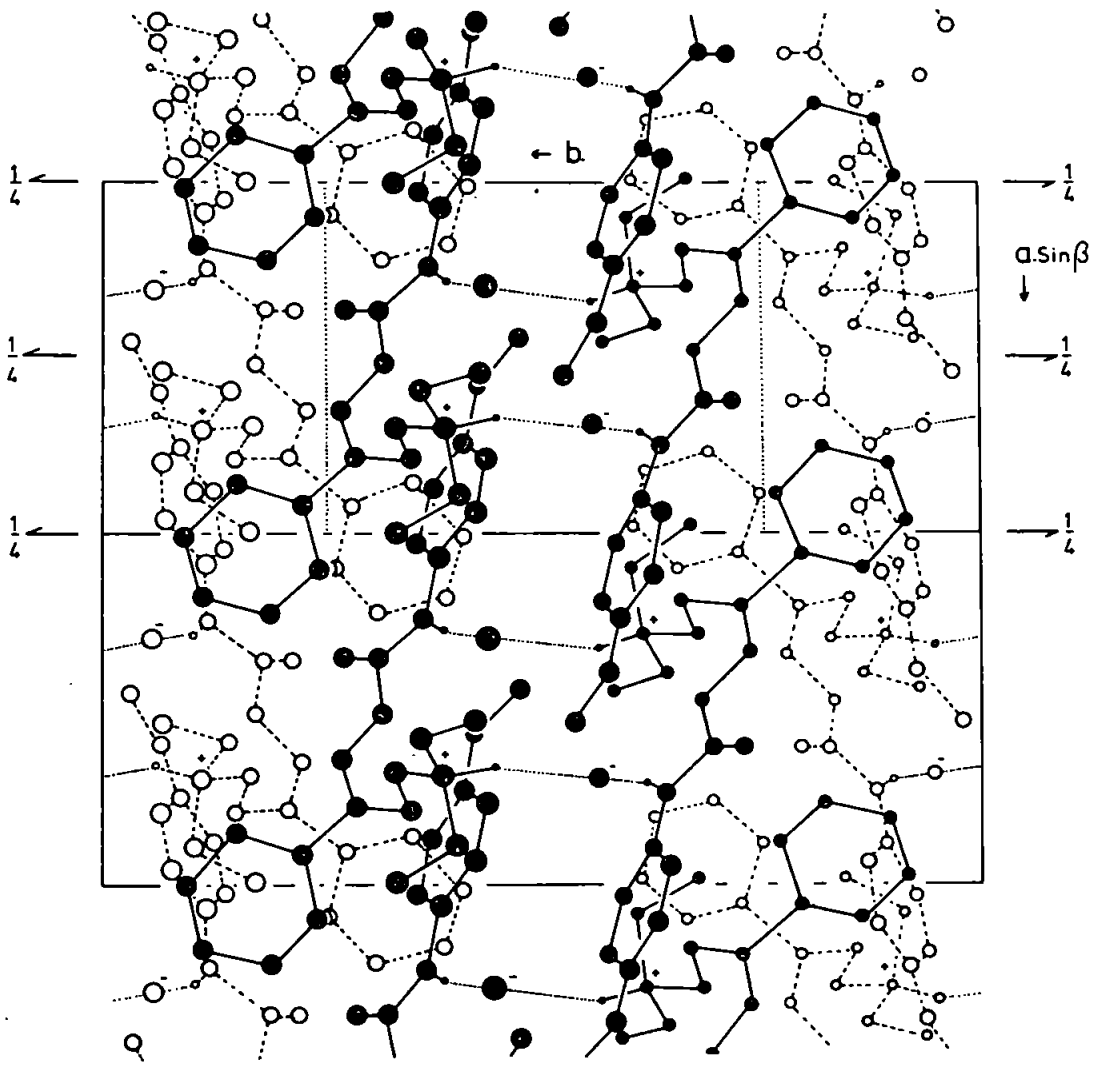


Fig 5·7 – Anidoxime: structure viewed along c-axis.

(i) Hydrogen Bonding

The principal binding forces in the crystal appear to be intermolecular N.....Cl hydrogen bonding between N_9 and N_{23} of centrosymmetrically related pairs of molecules, as represented in Fig 5.7 by dotted lines. The bonding, between one pair of molecules, as viewed from the positive a- and c- directions respectively is illustrated in Fig 5.8a and b.

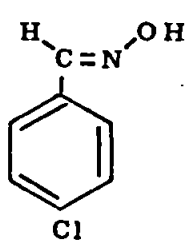
The $N9_A$ - $C1_A^-$ distance is 3.285 Å and the $\overset{+}{N}23_B$ - $C1_A^-$ distance is 3.239 Å, these values being slightly greater than the $\overset{+}{N}$ - $C1^-$ distance of 3.10 ± .08 Å quoted for the dihydrochloride of hydrazine, $N_2H_4 \cdot 2HCl$, in ref 8, Vol III 1968, p 273.

(ii) Thermal Anistropy

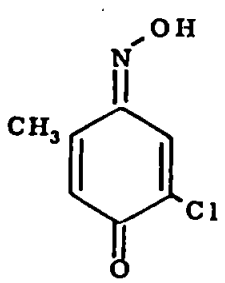
The ORTEP diagram of the molecule, Fig 5.9 clearly shows the thermal anisotropy of the non aromatic atoms, particularly O11, C25 and C27.

(iii) The Oxime Function

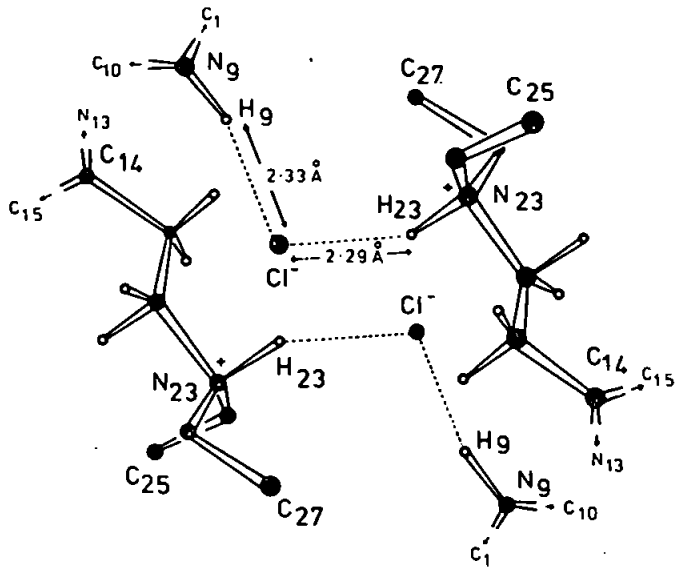
The phenyl ring at C_{14} and the oxime ester substituent at N_{13} are in the E configuration with the C = N bond lengths of 1.272(7) Å lying between the values of 1.26 Å for anti-p-chlorobenzaldoxime 12 and 1.28 Å for 5-chloro-2 methyl-p-benzoquinone oxime 13, which are quoted in Interatomic Distances Supplement, [82] p M1385.



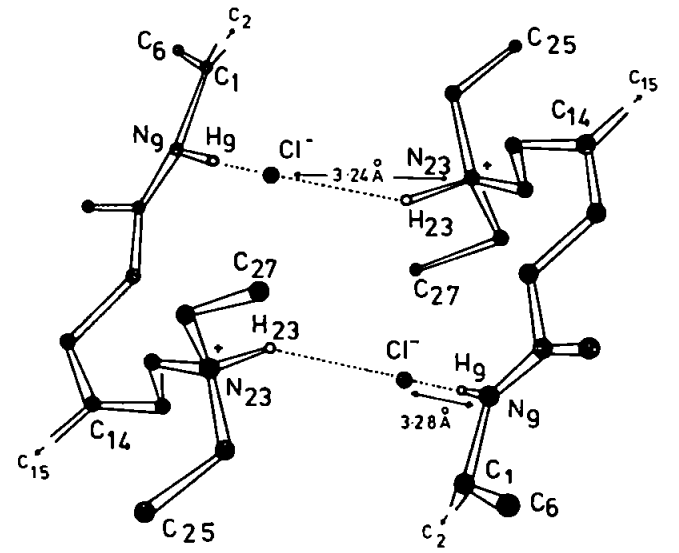
12.



13.



Viewed along a-axis, from +a



Viewed along c-axis, from +c

Fig 5·8 – Hydrogen bonding in Anidoxime

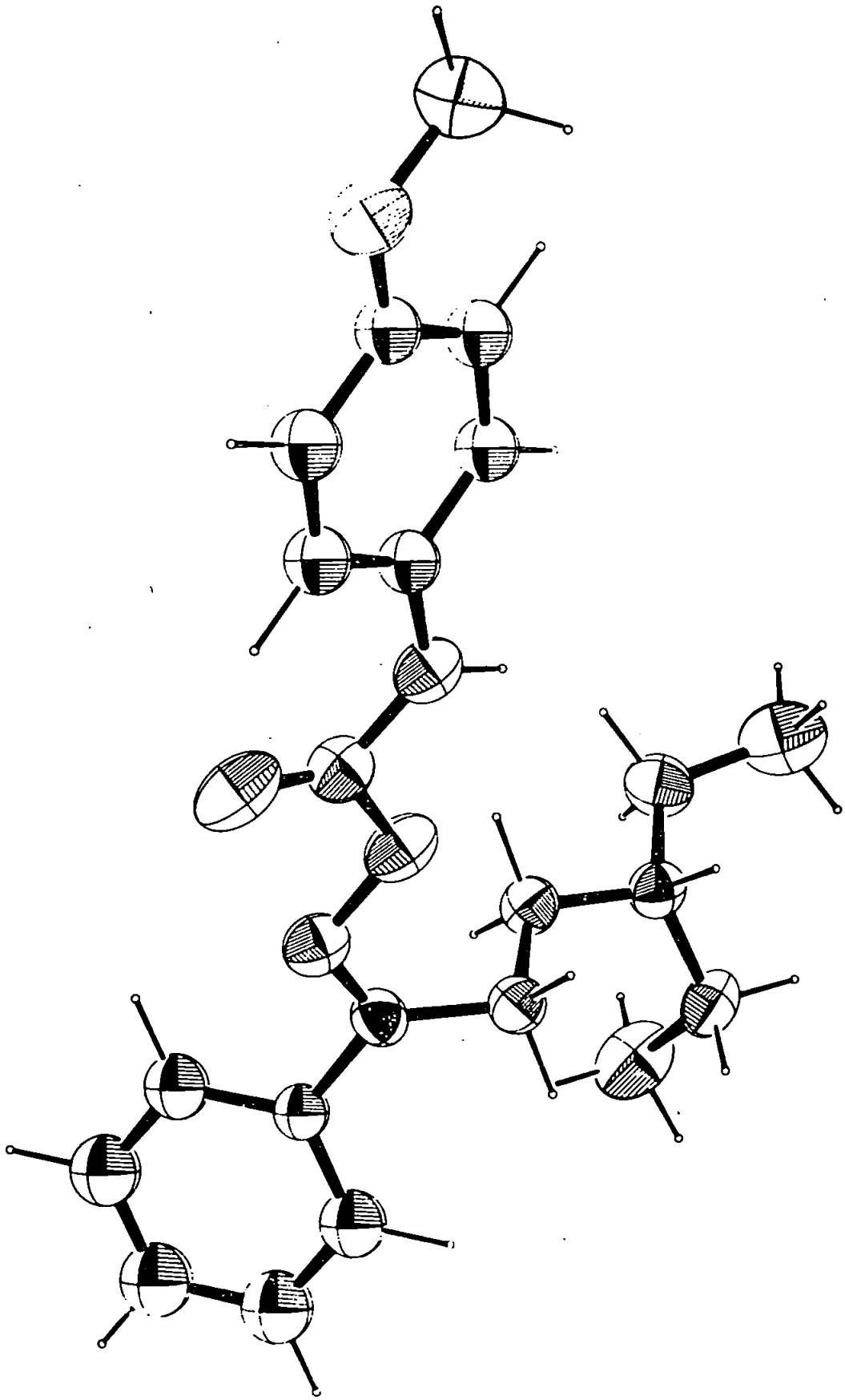


Fig 5·9 - 'ORTEP' plot of anidoxime molecule.

(iv) Carbamoyl Function Bond Lengths

a. $C_{10} - O_{11}$ The carbonyl bond length at 1.179(7) Å is less than that quoted for esters of 1.23 ± .01 Å in ref 8, Vol III p 276, or the average value of 1.233 ± .005 Å quoted in ref 82 p S215.

b. $C_{10} - O_{12}$ At 1.390(6) Å this bond is slightly shorter than the 1.43 ± .01 Å value given in ref 5, for (sp_3) - O bonding.

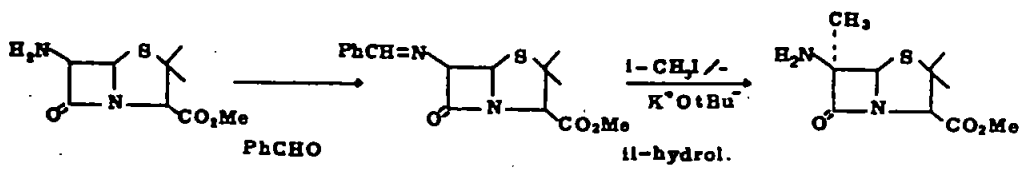
c. $C_{10} - N_9$ The value 1.350(6) Å is reasonably close to that reported for formamide, of 1.343 ± .007 Å, ref 82 p M645.

APPENDIX A

Synthetic Routes to 6α-substituted Penicillins and Cephalosporins

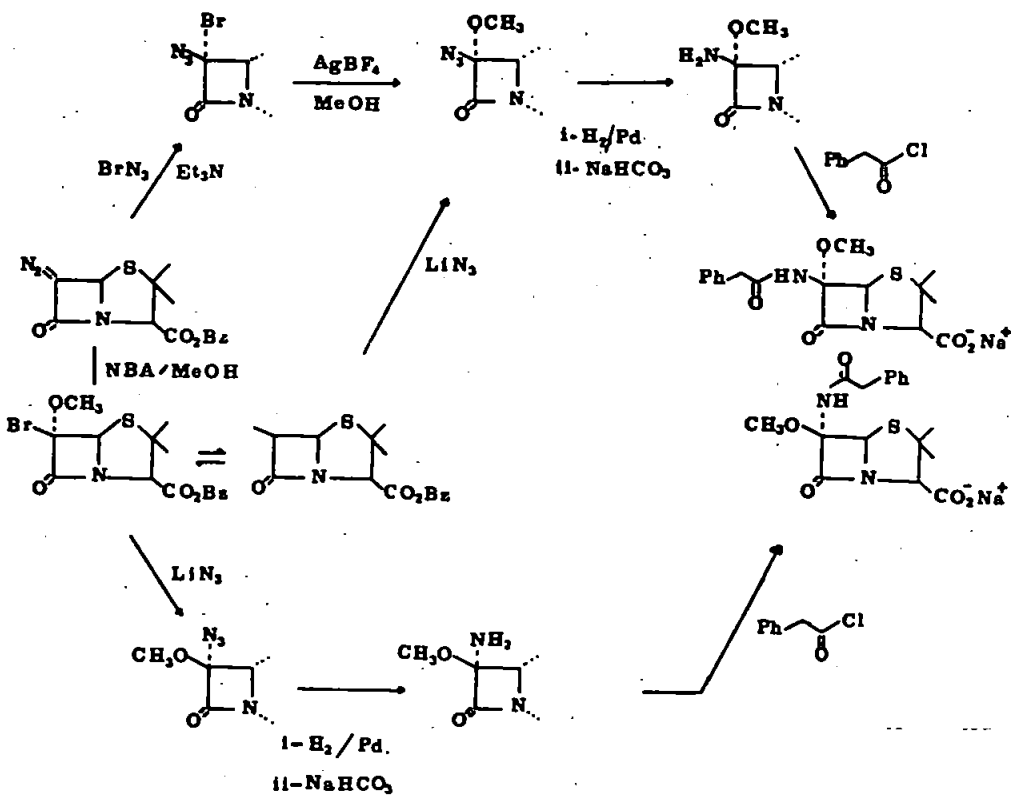
(a) Some interesting methods have been devised for the synthesis of these compounds, full details of which are available in the references cited. By way of comparison, the reaction sequences of some of the more significant are outlined below, along with the method of preparation of Benzyl-6α-benzyl-6β-isocyano penicillanate.

1. Method of E. H. W. Bohme et al, 1971 [27], 1973 [28] : Activation by Schiff base - Scheme 1.



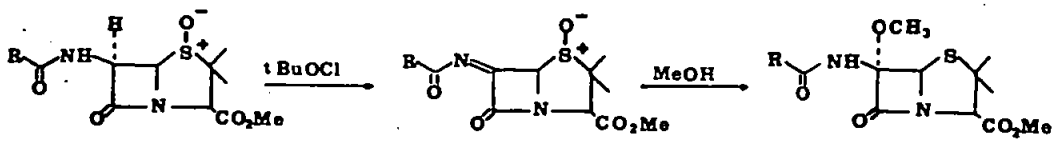
Scheme 1.

2. Method of L. D. Cama et al, 1971 [26] : Utilization of bromine azide with diazocarbonyl compounds - Scheme 2.



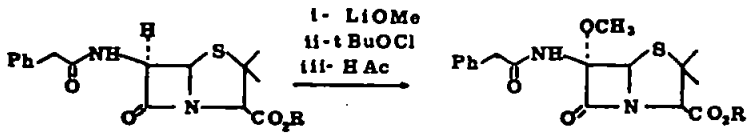
Scheme 2.

3. Method of Baldwin et al, 1973 [22] : Addition of methanol to an acylamine generated via t-butyl hypochlorite. (Thiazolidine sulphur protected by conversion to suphone or sulphoxide) - Scheme 3.



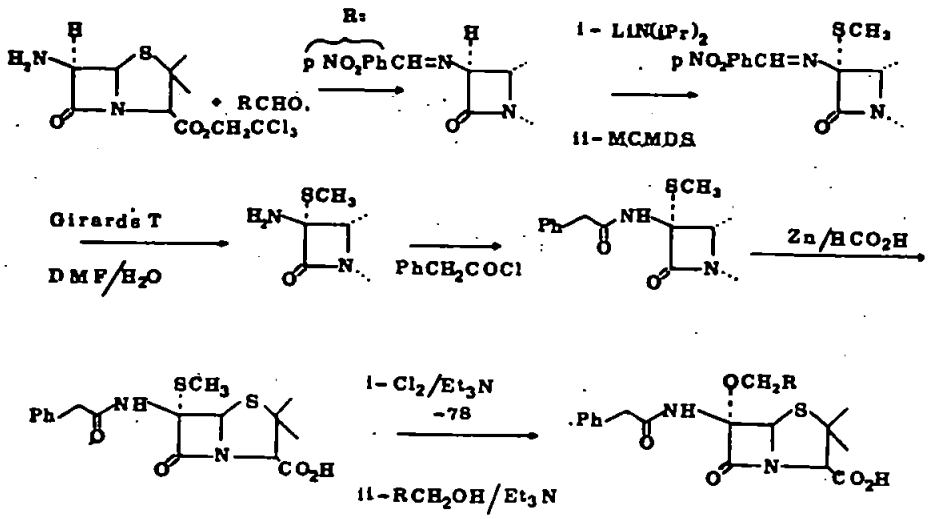
Scheme 3.

4. Method of Koppel and Koehler 1973, [38] : Use of $LiOCH_3$ to generate amide anion, followed by reaction with t-butyl hypochlorite - Scheme 4.



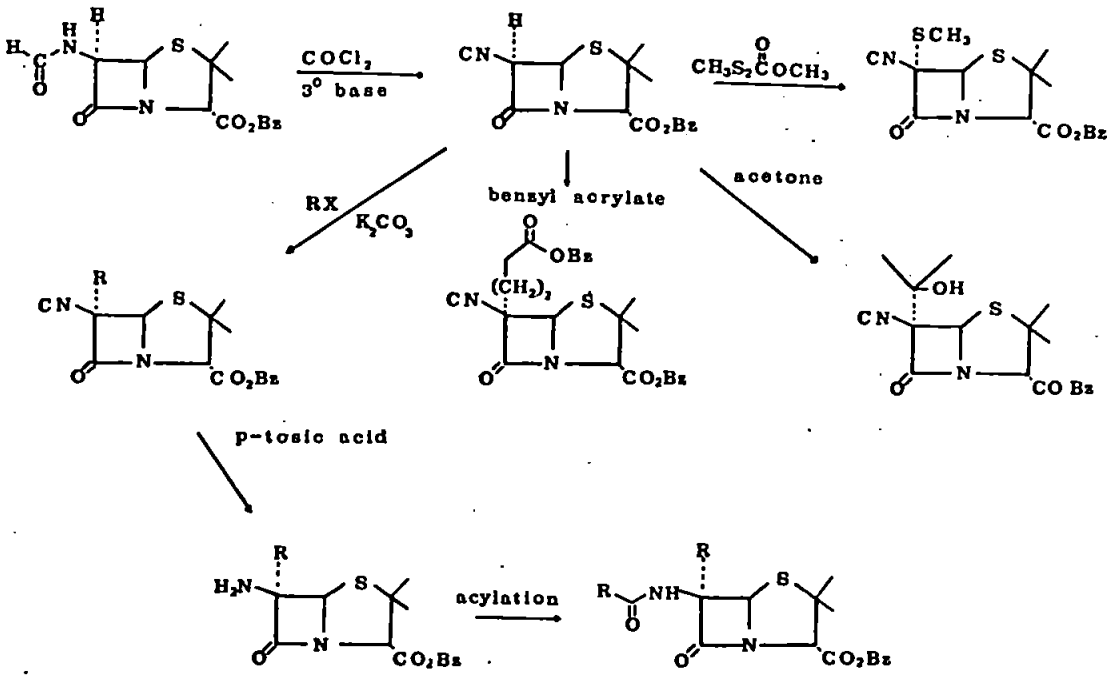
Scheme 4.

5. Method of Spitzer and Goodson 1973, [30] : Replacement of $-SCH_3$ by $-OCH_2R$ - Scheme 5.



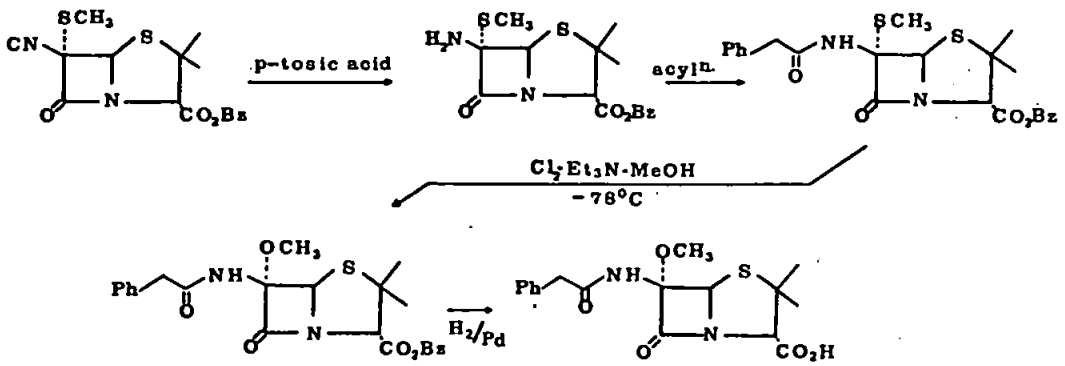
Scheme 5.

6. Method of Bentley and Clayton, 1974 [21], via isocyanide route - Scheme 6a.



Scheme 6a.

Support for the assignment of the 6α configuration to compounds derived via this sequence was given by the preparation of 6α-methoxy-phenylacetamido-penicillanic acid, identical with the product obtained via the diazocarbonyl route of Cama et al.

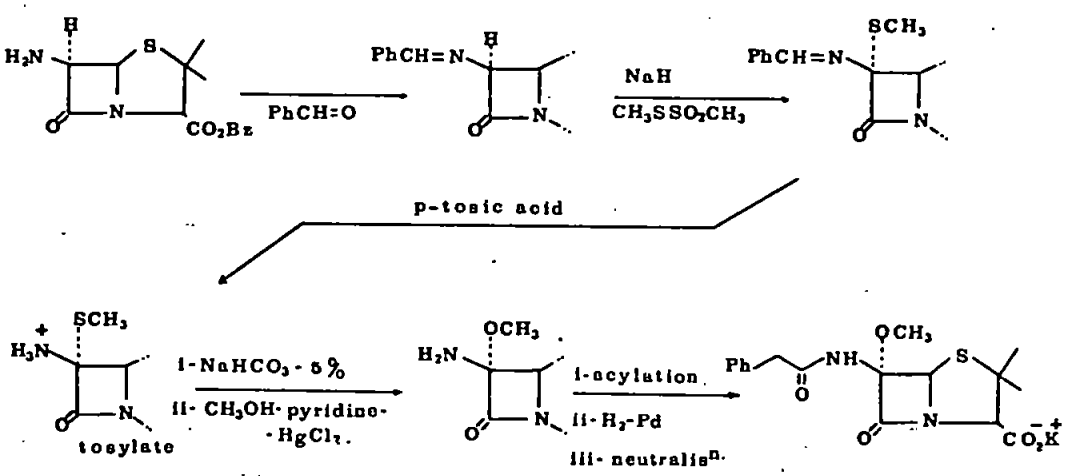


Scheme 6b.

Among the compounds prepared by these workers, was 6α-methoxy ampicillin.

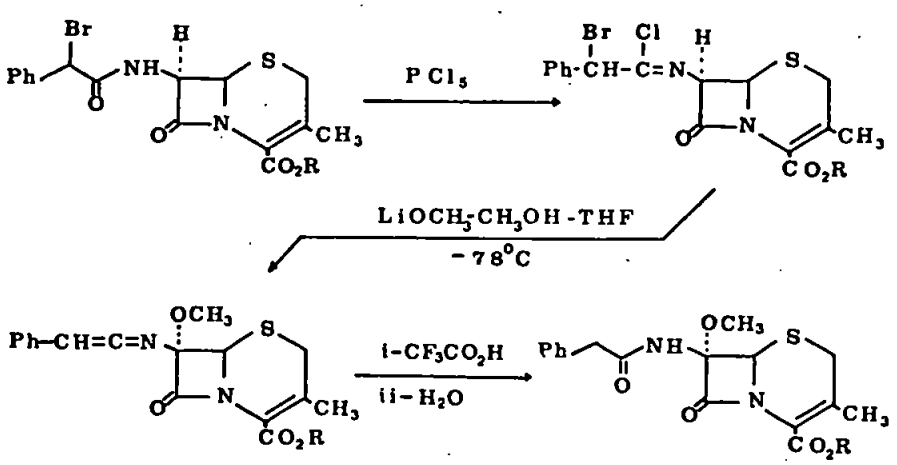
Evaluation of this compound revealed a minimum inhibitory concentration of 125 μg/ml compared with 0.05 μg/ml for benzyl penicillin. Introduction of the 6α-methoxy function appears to have resulted in the same de-activating effects encountered by other workers.

7. Method of Frazee and Hoover 1973 [43] - Scheme 7.



Scheme 7.

8. Method of Sugimura et al, 1976 [44] : High yield method, via elimination to form imino intermediate, followed by stereospecific methoxylation - Scheme 8.



Scheme 8.

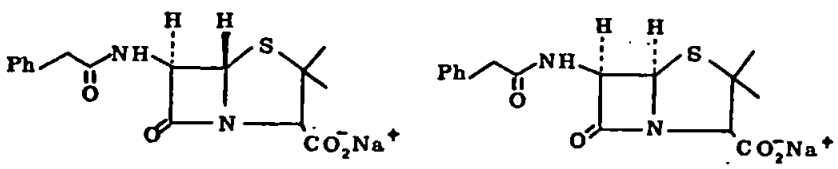
In relation to the conversion of penicillins into cephalosporins, a convenient high yield method for the deoxygenation of cephalosporin and penicillin sulfoxides, using P_2S_5 has been reported by Micetich, 1976 [45].

The foregoing summary is necessarily brief, and further information about the recent chemistry of penicillins and cephalosporins may be found in the review of Sammes, 1976 [46].

(b) The great importance of stereochemistry in relation to activity of penicillins, was recently demonstrated by Busson and Vanderhaeghe 1976 [47], who found that the sodium salt of 5-epibenzyl penicillin,

(1a)- had activity of less than 0.1% of natural benzyl penicillin,

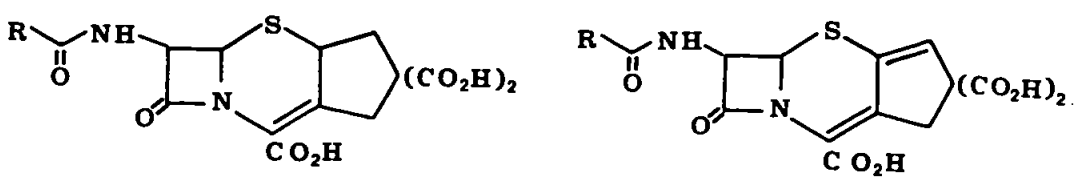
(1b)- against staphylococcus aureus.



(a) (b)

1.

In conclusion, it is apparent that antibacterial activity of the cephem nucleus survives structural modifications of a major nature. The tricyclic cephalosporins, for example (2a) and (2b), described by Spry 1975 [83], were claimed to inhibit growth of gram positive organisms in unspecified warm blooded animals, at non toxic dose levels in the range 50 - 500 mg/kg.



(a) (b)

2.

As the patent application [83] contains comparative zone inhibition data for only a few compounds, the significance of the slightly greater inhibition by the diene (2b) relative to the didehydro analogue (2a) may not be assessed. Should there prove to be a general potency difference in this direction between other pairs of analogues differing only in this way, such differences might be accounted for in terms of relative stabilization of the canonical forms (c) and (d), in Fig A1. In (d) the second double bond constitutes an electron-poor region adjacent to the formal delocalization site, and the additional canonical form (e) may contribute to resonance, further reducing any contribution from β- lactam resonance, relative to normal amides.

As discussed in Chapters 4 and 5, greater activity usually attends reduced β- lactam resonance stabilization in fused ring compounds.

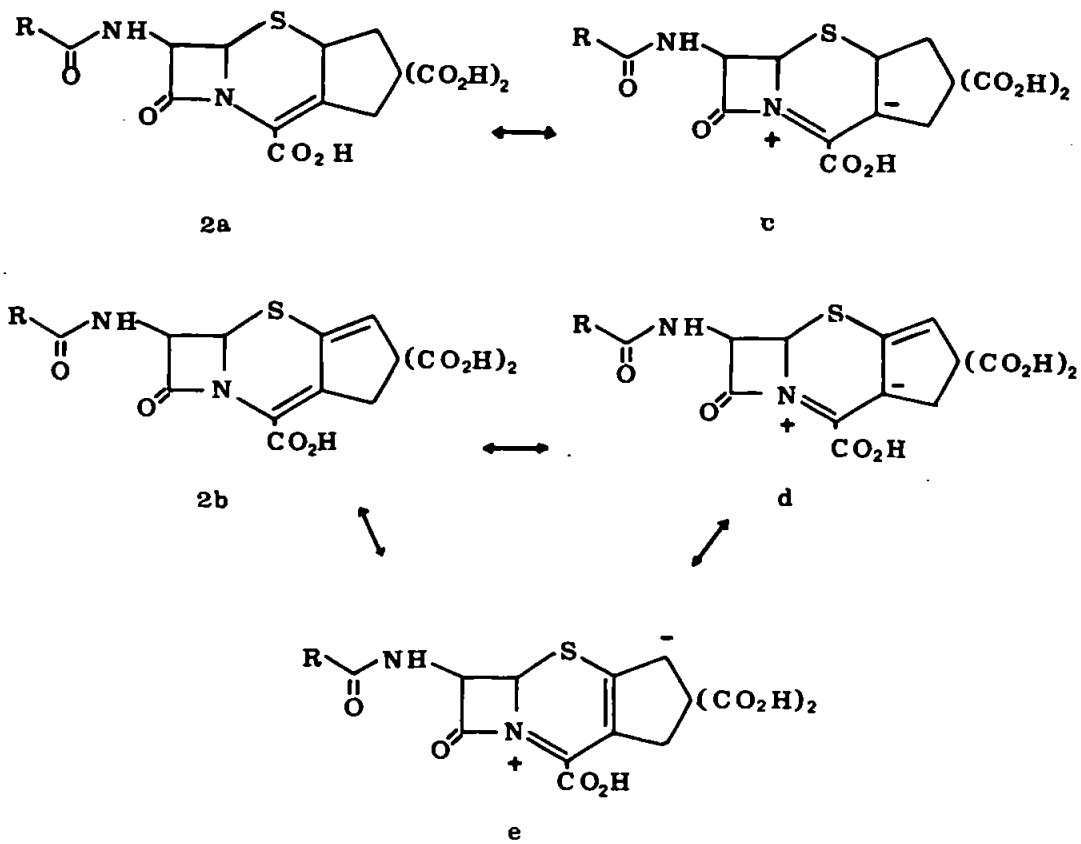


Fig A, Resonance in tricyclic cephalosporins

APPENDIX B

TABLE XVI

List of Structure Factors for Benzyl 6α -benzyl 6β - isocyanopenicillanate, BRL 11827

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR HERGE SPLIT LEVELS - isocyanopenicillanate

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	1	0	578	528	3	8	0	265	230	-2	2	1	348	316	0	5	1	452	463	1	8	1	485	462
3	1	0	104	101	4	8	0	128	106	-1	2	1	384	361	1	5	1	783	677	2	8	1	117	129
4	1	0	165	131	5	8	0	158	129	0	2	1	269	256	2	5	1	91	103	3	8	1	168	178
2	2	0	456	421	1	9	0	201	223	1	2	1	388	358	3	5	1	131	121	4	8	1	140	167
3	2	0	147	149	2	9	0	150	123	2	2	1	340	317	4	5	1	199	199	5	8	1	138	128
4	2	0	129	139	3	9	0	202	194	3	2	1	132	150	5	5	1	109	103	-5	9	1	50	23
5	2	0	65	80	0	10	0	280	266	4	2	1	160	157	-5	6	1	154	151	-4	9	1	122	117
1	3	0	1375	1508	1	10	0	227	203	5	2	1	59	44	-4	6	1	115	138	-3	9	1	245	260
2	3	0	417	336	2	10	0	87	90	-5	3	1	151	176	-3	6	1	120	112	-2	9	1	355	340
3	3	0	92	86	3	10	0	127	121	-4	3	1	182	185	-2	6	1	115	112	2	9	1	352	348
5	3	0	51	41	5	10	0	67	64	-3	3	1	529	589	-1	6	1	191	172	3	9	1	247	258
0	4	0	1167	1034	3	11	0	85	72	-2	3	1	202	135	0	6	1	177	156	4	9	1	115	126
1	4	0	243	259	1	12	0	360	370	-1	3	1	314	294	1	6	1	190	171	-3	10	1	107	92
2	4	0	576	612	2	12	0	141	147	0	3	1	202	215	2	6	1	126	113	-1	10	1	220	218
4	4	0	77	44	4	12	0	90	91	1	3	1	344	267	3	6	1	119	115	1	10	1	228	217
5	4	0	288	243	5	12	0	56	62	2	3	1	189	171	4	6	1	123	136	3	10	1	105	91
1	5	0	745	649	2	13	0	122	133	3	3	1	530	586	5	6	1	152	151	-4	11	1	229	210
2	5	0	204	211	0	14	0	88	88	4	3	1	193	177	-5	7	1	112	97	-3	11	1	184	166
3	5	0	254	268	1	14	0	285	311	5	3	1	175	161	-4	7	1	245	253	-2	11	1	230	243
4	5	0	56	52	5	14	0	49	54	-5	4	1	64	58	-3	7	1	116	109	2	11	1	245	250
5	5	0	93	56	2	15	0	197	195	-4	4	1	195	198	-2	7	1	629	621	3	11	1	172	165
0	6	0	592	603	3	15	0	136	111	-3	4	1	88	98	-1	7	1	642	639	4	11	1	226	219
1	6	0	218	164	0	18	0	141	122	-2	4	1	483	491	0	7	1	278	297	-2	12	1	148	141
2	6	0	204	190	3	18	0	71	66	-1	4	1	1139	1035	1	7	1	647	627	2	12	1	148	141
3	6	0	296	296	3	0	1	100	87	0	4	1	1082	1148	2	7	1	413	411	-4	13	1	170	177
4	6	0	153	122	4	0	1	227	276	1	4	1	1148	1032	3	7	1	121	114	0	13	1	106	87
5	6	0	286	257	-4	1	1	55	42	2	4	1	490	491	4	7	1	265	241	4	13	1	177	172
1	7	0	295	281	-2	1	1	244	224	3	4	1	84	99	5	7	1	104	104	-3	14	1	93	93
2	7	0	142	119	2	1	1	225	221	4	4	1	198	198	-5	8	1	128	130	3	14	1	83	93
3	7	0	290	318	4	1	1	53	43	5	4	1	55	59	-4	8	1	149	165	2	0	2	195	235
4	7	0	70	79	5	1	1	257	257	-5	5	1	122	98	-3	8	1	164	176	4	0	2	125	112
0	8	0	285	222	-5	2	1	60	43	-4	5	1	193	203	-2	8	1	118	129	5	0	2	67	62
1	8	0	350	321	-4	2	1	156	155	-3	5	1	139	133	-1	8	1	504	461	-5	1	2	121	114
2	8	0	213	189	-3	2	1	134	150	-1	5	1	768	688	0	8	1	173	148	-4	1	2	211	219

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR HERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-3	1	2	102	100	0	4	2	464	439	3	7	2	90	96	1	14	2	244	258	0	3	3	34	63
-2	1	2	377	430	1	4	2	423	389	4	7	2	207	223	2	14	2	178	171	1	3	3	381	352
-1	1	2	829	1076	2	4	2	648	679	5	7	2	90	93	3	14	2	79	69	2	3	3	359	341
1	1	2	730	1076	3	4	2	96	93	-5	8	2	100	93	-3	15	2	108	99	3	3	3	333	363
2	1	2	422	472	4	4	2	193	162	-4	8	2	144	135	0	15	2	98	89	4	3	3	181	175
3	1	2	93	99	5	4	2	100	83	-3	8	2	263	273	3	15	2	108	98	5	3	3	167	133
4	1	2	228	217	-5	5	2	165	168	-2	8	2	146	126	-3	16	2	129	110	-5	4	3	117	109
5	1	2	110	116	-4	5	2	136	151	-1	8	2	463	438	3	16	2	130	111	-4	4	3	153	151
-5	2	2	48	46	-3	5	2	53	49	1	8	2	461	438	0	20	2	90	77	-3	4	3	83	68
-4	2	2	130	125	-2	5	2	184	176	2	8	2	145	125	1	0	3	420	499	-2	4	3	177	189
-3	2	2	261	326	-1	5	2	265	247	3	8	2	274	285	2	0	3	173	170	-1	4	3	1048	914
-2	2	2	585	618	0	5	2	171	125	4	8	2	166	132	3	0	3	122	127	0	4	3	1119	1158
-1	2	2	221	212	1	5	2	279	245	5	8	2	105	93	-5	1	3	189	161	1	4	3	960	915
1	2	2	213	208	2	5	2	199	180	-2	9	2	205	192	-4	1	3	65	69	2	4	3	195	192
2	2	2	610	609	3	5	2	56	51	-1	9	2	189	193	-2	1	3	217	234	3	4	3	83	72
3	2	2	258	326	4	5	2	133	153	0	9	2	268	257	-1	1	3	564	460	4	4	3	163	152
4	2	2	143	135	5	5	2	171	167	1	9	2	190	191	1	1	3	400	497	5	4	3	119	106
5	2	2	47	47	-5	6	2	218	175	2	9	2	200	189	2	1	3	231	236	-5	5	3	76	58
-5	3	2	56	56	-4	6	2	141	157	-4	10	2	80	80	4	1	3	69	69	-4	5	3	107	120
-4	3	2	190	207	-3	6	2	160	156	-3	10	2	138	140	5	1	3	190	165	-3	5	3	155	152
-3	3	2	372	396	-2	6	2	162	144	-1	10	2	378	376	-4	2	3	84	88	-2	5	3	221	232
-2	3	2	208	209	-1	6	2	100	89	1	10	2	408	360	-3	2	3	144	136	-1	5	3	646	593
-1	3	2	421	363	2	6	2	144	125	3	10	2	141	142	-2	2	3	142	163	0	5	3	754	737
0	3	2	681	649	3	6	2	149	145	0	11	2	164	166	-1	2	3	418	371	1	5	3	639	587
1	3	2	435	364	4	6	2	148	150	-5	12	2	71	30	0	2	3	213	253	2	5	3	245	252
2	3	2	216	211	5	6	2	214	178	-1	12	2	216	212	1	2	3	410	375	3	5	3	137	135
3	3	2	357	395	-5	7	2	93	94	0	12	2	143	129	2	2	3	159	162	4	5	3	122	111
4	3	2	179	206	-4	7	2	210	221	1	12	2	198	221	3	2	3	144	136	5	5	3	75	58
5	3	2	53	56	-3	7	2	94	98	5	12	2	87	77	4	2	3	91	84	-5	6	3	84	35
-5	4	2	103	75	-2	7	2	220	199	-3	13	2	126	138	-5	3	3	158	143	-3	6	3	195	197
-4	4	2	177	169	-1	7	2	205	187	0	13	2	171	139	-4	3	3	171	177	-2	6	3	262	259
-3	4	2	99	101	0	7	2	263	248	3	13	2	123	137	-3	3	3	335	362	-1	6	3	471	433
-2	4	2	620	672	1	7	2	202	188	-2	14	2	181	176	-2	3	3	323	317	0	6	3	179	150
-1	4	2	419	387	2	7	2	214	199	-1	14	2	268	260	-1	3	3	404	325	1	6	3	476	437

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR MERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	6	3	260	261	3	10	3	82	89	0	1	4	595	804	5	4	4	146	138	1	8	4	154	99
3	6	3	107	110	-4	11	3	111	112	2	1	4	215	217	-4	5	4	98	96	2	8	4	394	372
4	6	3	54	56	-3	11	3	211	218	3	1	4	192	205	-3	5	4	87	82	3	8	4	211	214
5	6	3	88	81	-2	11	3	205	209	4	1	4	149	126	-1	5	4	186	156	4	8	4	130	115
-5	7	3	173	174	0	11	3	166	170	5	1	4	135	141	0	5	4	411	396	5	8	4	133	140
-4	7	3	77	90	2	11	3	201	209	-5	2	4	38	38	1	5	4	174	156	-1	9	4	280	269
-3	7	3	136	128	3	11	3	215	220	-4	2	4	199	170	3	5	4	86	83	0	9	4	318	334
-2	7	3	333	312	4	11	3	116	112	-3	2	4	80	73	4	5	4	106	94	1	9	4	271	265
-1	7	3	229	255	-3	12	3	90	80	-2	2	4	576	628	-5	6	4	174	128	2	9	4	125	128
0	7	3	566	552	-2	12	3	123	111	-1	2	4	446	474	-4	6	4	150	142	-5	10	4	100	92
1	7	3	249	247	0	12	3	162	153	0	2	4	592	658	-3	6	4	140	159	-3	10	4	152	149
2	7	3	353	333	2	12	3	123	109	1	2	4	446	467	-2	6	4	183	180	-2	10	4	189	179
3	7	3	114	115	3	12	3	84	81	2	2	4	576	608	-1	6	4	450	423	-1	10	4	155	152
4	7	3	90	78	-4	13	3	138	144	3	2	4	70	66	0	6	4	447	440	0	10	4	230	236
5	7	3	209	179	-2	13	3	154	170	4	2	4	199	175	1	6	4	439	421	1	10	4	131	169
-4	8	3	152	140	0	13	3	141	136	-4	3	4	84	94	2	6	4	201	196	2	10	4	181	177
-3	8	3	97	95	2	13	3	188	188	-3	3	4	121	133	3	6	4	146	168	3	10	4	168	147
-1	8	3	283	231	4	13	3	122	146	-2	3	4	367	376	4	6	4	167	134	5	10	4	99	90
1	8	3	274	230	-4	14	3	89	88	-1	3	4	422	385	5	6	4	163	134	-3	11	4	99	98
3	8	3	104	98	-4	15	3	65	79	0	3	4	614	644	-5	7	4	145	148	2	11	4	135	116
4	8	3	145	139	-2	15	3	121	125	1	3	4	432	381	-4	7	4	90	88	3	11	4	98	96
-4	9	3	110	91	0	15	3	85	104	2	3	4	386	380	-2	7	4	441	428	-5	12	4	56	66
-3	9	3	147	162	2	15	3	130	133	3	3	4	118	131	-1	7	4	237	226	-3	12	4	181	177
-2	9	3	497	482	4	15	3	67	82	4	3	4	93	91	0	7	4	73	43	-1	12	4	313	318
-1	9	3	210	208	0	17	3	109	98	-5	4	4	157	131	1	7	4	237	230	1	12	4	318	325
1	9	3	223	202	0	19	3	72	68	-4	4	4	167	168	2	7	4	445	424	3	12	4	174	167
2	9	3	499	476	1	0	4	156	170	-3	4	4	340	343	4	7	4	85	89	5	12	4	77	62
3	9	3	147	160	2	0	4	472	539	-2	4	4	292	303	5	7	4	152	147	-3	13	4	119	108
4	9	3	113	85	3	0	4	165	163	-1	4	4	385	367	-5	8	4	153	139	-1	13	4	243	247
-4	10	3	132	144	4	0	4	313	343	0	4	4	87	71	-4	8	4	122	123	0	13	4	101	97
-3	10	3	83	88	-5	1	4	133	143	1	4	4	393	352	-3	8	4	202	198	1	13	4	238	249
-1	10	3	164	172	-4	1	4	138	127	2	4	4	296	301	-2	8	4	384	363	3	13	4	111	107
0	10	3	247	228	-3	1	4	200	207	3	4	4	316	338	-1	8	4	136	121	-5	14	4	31	39
1	10	3	168	171	-2	1	4	212	222	4	4	4	159	183	0	8	4	279	264	-3	14	4	188	180

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR MERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-2	14	4	116	125	2	3	5	96	96	4	6	5	109	109	2	10	5	170	172	-4	2	6	347	297
3	14	4	185	179	3	3	5	224	235	-5	7	5	139	124	3	10	5	167	161	-3	2	6	76	85
0	16	4	147	158	4	3	5	116	111	-4	7	5	121	123	-5	11	5	41	24	-2	2	6	209	259
1	0	5	176	160	5	3	5	100	74	-3	7	5	180	174	-4	11	5	93	88	-1	2	6	308	305
2	0	5	303	339	-5	4	5	57	56	-2	7	5	100	111	-2	11	5	287	275	0	2	6	52	40
3	0	5	340	398	-4	4	5	68	70	-1	7	5	397	372	-1	11	5	160	151	1	2	6	331	300
-5	1	5	215	199	-3	4	5	189	192	0	7	5	370	383	1	11	5	165	149	2	2	6	231	272
-4	1	5	88	91	-2	4	5	366	371	1	7	5	408	374	2	11	5	305	289	3	2	6	70	79
-3	1	5	190	217	-1	4	5	127	134	3	7	5	170	161	4	11	5	95	84	4	2	6	314	303
-2	1	5	223	219	0	4	5	382	406	4	7	5	132	114	-4	12	5	88	89	-5	3	6	100	38
-1	1	5	738	837	1	4	5	129	135	5	7	5	140	125	-3	12	5	124	128	-3	3	6	99	92
0	1	5	124	135	2	4	5	374	366	-5	8	5	73	62	-1	12	5	223	219	-2	3	6	310	339
1	1	5	720	832	3	4	5	174	188	-3	8	5	143	143	0	12	5	93	90	-1	3	6	338	353
2	1	5	226	220	4	4	5	70	67	-2	8	5	134	127	1	12	5	206	218	0	3	6	445	509
3	1	5	165	192	5	4	5	64	53	-1	8	5	161	146	3	12	5	127	129	1	3	6	330	346
4	1	5	88	89	-5	5	5	148	130	0	8	5	271	277	4	12	5	88	90	2	3	6	309	303
5	1	5	216	191	-4	5	5	248	229	1	8	5	162	146	-2	13	5	132	151	3	3	6	94	93
-5	2	5	59	69	-3	5	5	220	207	2	8	5	137	131	0	13	5	280	279	5	3	6	96	89
-4	2	5	61	53	-2	5	5	137	140	3	8	5	142	141	2	13	5	147	164	-5	4	6	142	124
-3	2	5	88	110	-1	5	5	340	348	4	8	5	64	61	0	15	5	163	177	-4	4	6	177	167
-2	2	5	58	70	0	5	5	433	476	5	8	5	63	65	1	0	6	539	621	-3	4	6	109	110
-1	2	5	164	145	1	5	5	351	343	-3	9	5	71	63	2	0	6	164	158	-2	4	6	612	643
0	2	5	835	928	2	5	5	145	141	-2	9	5	273	288	3	0	6	198	217	-1	4	6	325	354
1	2	5	175	140	3	5	5	207	199	-1	9	5	178	177	4	0	6	433	437	1	4	6	356	343
3	2	5	87	111	4	5	5	265	220	0	9	5	150	147	5	0	6	70	68	2	4	6	633	631
4	2	5	65	49	5	5	5	152	134	1	9	5	197	168	-5	1	6	80	68	3	4	6	108	112
5	2	5	62	67	-4	6	5	102	112	2	9	5	261	283	-3	1	6	209	199	4	4	6	179	173
-5	3	5	102	84	-3	6	5	45	47	4	9	5	78	86	-2	1	6	322	330	5	4	6	125	132
-4	3	5	112	111	-2	6	5	236	243	-4	10	5	72	73	-1	1	6	387	436	-5	5	6	122	131
-3	3	5	241	244	-1	6	5	147	163	-3	10	5	164	160	0	1	6	162	202	-3	5	6	172	163
-2	3	5	105	109	0	6	5	175	192	-2	10	5	172	174	1	1	6	400	431	-2	5	6	103	132
-1	3	5	321	344	1	6	5	148	161	-1	10	5	171	163	2	1	6	334	323	-1	5	6	216	213
0	3	5	340	351	2	6	5	259	248	0	10	5	84	77	3	1	6	206	202	0	5	6	364	361
1	3	5	339	320	3	6	5	58	50	1	10	5	169	162	5	1	6	79	71	1	5	6	214	214

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR MERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	5	6	110	103	-5	10	6	92	103	4	1	7	68	71	5	4	7	100	88	-1	9	7	174	190
3	5	6	163	165	-3	10	6	220	224	5	1	7	133	113	-5	5	7	170	163	1	9	7	180	189
5	5	6	120	102	-1	10	6	225	241	-5	2	7	91	70	-4	5	7	86	107	2	9	7	197	195
-4	6	6	86	75	1	10	6	214	246	-4	2	7	67	53	-3	5	7	200	206	4	9	7	127	138
-3	6	6	130	110	3	10	6	232	234	-3	2	7	109	104	-2	5	7	119	149	-2	10	7	132	130
-2	6	6	365	351	5	10	6	102	97	-2	2	7	239	252	0	5	7	269	270	0	11	7	489	481
-1	6	6	382	352	-1	11	6	188	180	-1	2	7	285	313	2	5	7	137	155	2	12	7	127	125
0	6	6	169	183	0	11	6	106	88	0	2	7	196	237	3	5	7	184	196	3	12	7	74	75
1	6	6	391	355	1	11	6	206	184	1	2	7	288	305	4	5	7	110	96	0	13	7	340	319
2	6	6	377	356	-5	12	6	72	75	2	2	7	248	253	5	5	7	178	162	0	14	7	92	87
3	6	6	126	109	-3	12	6	139	157	3	2	7	118	110	-4	6	7	112	127	0	15	7	114	128
4	6	6	90	72	0	12	6	192	187	4	2	7	73	52	-3	6	7	119	118	4	15	7	57	77
-4	7	6	90	95	3	12	6	134	151	5	2	7	96	67	-2	6	7	83	76	0	0	8	334	272
-3	7	6	106	110	5	12	6	67	76	-5	3	7	142	117	-1	6	7	344	340	2	0	8	155	170
-2	7	6	157	156	0	13	6	107	82	-4	3	7	69	62	0	6	7	201	196	3	0	8	269	269
-1	7	6	173	156	-3	14	6	150	153	-3	3	7	242	246	1	6	7	358	338	4	0	8	336	330
0	7	6	127	125	3	14	6	144	149	-2	3	7	99	95	3	6	7	114	116	5	0	8	82	100
1	7	6	183	156	-3	16	6	89	78	-1	3	7	482	486	4	6	7	124	122	-4	1	8	89	88
2	7	6	171	158	0	16	6	143	139	0	3	7	326	436	-5	7	7	100	99	-3	1	8	198	185
3	7	6	111	115	3	16	6	89	83	1	3	7	474	483	-4	7	7	73	65	-2	1	8	102	97
4	7	6	93	94	3	18	6	47	56	2	3	7	110	100	-3	7	7	79	75	-1	1	8	191	186
-4	8	6	77	89	1	0	7	257	268	3	3	7	241	255	-2	7	7	325	321	0	1	8	196	178
-3	8	6	277	270	2	0	7	181	190	4	3	7	74	66	2	7	7	329	320	1	1	8	185	184
-2	8	6	306	299	3	0	7	47	54	5	3	7	148	112	4	7	7	70	72	2	1	8	107	98
-1	8	6	284	330	5	0	7	85	86	-5	4	7	86	92	5	7	7	99	99	3	1	8	187	186
1	8	6	294	320	-5	1	7	124	117	-4	4	7	96	86	-3	8	7	101	99	4	1	8	81	93
2	8	6	311	301	-4	1	7	71	68	-3	4	7	203	199	-2	8	7	112	122	-4	2	8	287	264
3	8	6	271	276	-3	1	7	107	96	-2	4	7	160	176	-1	8	7	181	151	-3	2	8	112	97
4	8	6	100	81	-2	1	7	210	230	-1	4	7	333	336	0	8	7	136	150	-2	2	8	182	205
-3	9	6	114	124	-1	1	7	647	724	0	4	7	163	115	1	8	7	178	152	-1	2	8	118	105
-2	9	6	98	102	0	1	7	380	368	1	4	7	335	330	2	8	7	116	120	0	2	8	162	167
0	9	6	75	79	1	1	7	718	717	2	4	7	174	181	3	8	7	94	96	1	2	8	103	98
3	9	6	118	129	2	1	7	210	226	3	4	7	203	205	-4	9	7	143	130	2	2	8	219	219
4	9	6	104	97	3	1	7	116	115	4	4	7	96	83	-2	9	7	195	201	3	2	8	101	99

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR MERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
4	2	8	297	262	0	6	8	368	359	0	15	8	138	120	-1	3	9	360	351	4	6	9	98	107
-5	3	8	85	80	1	6	8	428	427	2	15	8	105	90	0	3	9	476	533	-5	7	9	86	85
-3	3	8	158	158	2	6	8	270	284	-3	16	8	95	92	1	3	9	348	360	-4	7	9	113	97
-2	3	8	285	285	4	6	8	77	75	3	16	8	105	94	2	3	9	172	153	-3	7	9	80	78
-1	3	8	224	258	-4	7	8	87	84	0	18	8	69	79	3	3	9	155	156	0	7	9	196	175
0	3	8	71	76	-3	7	8	216	234	2	0	9	146	172	4	3	9	109	128	3	7	9	83	89
1	3	8	244	253	3	7	8	208	238	4	0	9	190	186	5	3	9	163	132	4	7	9	102	98
2	3	8	294	280	4	7	8	95	84	5	0	9	66	45	-5	4	9	81	73	5	7	9	83	94
3	3	8	149	156	-3	8	8	145	144	-5	1	9	52	53	-4	4	9	57	57	-4	8	9	78	76
5	3	8	81	81	-2	8	8	192	187	-4	1	9	68	70	-2	4	9	204	214	-1	8	9	186	182
-5	4	8	64	66	-1	8	8	342	359	-3	1	9	255	246	-1	4	9	428	405	1	8	9	187	179
-4	4	8	167	183	0	8	8	160	171	-2	1	9	176	179	0	4	9	111	138	4	8	9	53	74
-3	4	8	86	88	1	8	8	324	367	-1	1	9	485	502	1	4	9	440	413	-3	9	9	79	75
-2	4	8	318	334	2	8	8	188	179	0	1	9	794	787	2	4	9	215	218	-2	9	9	213	199
-1	4	8	409	375	3	8	8	126	134	1	1	9	494	510	4	4	9	68	54	0	9	9	87	103
0	4	8	236	253	-4	9	8	106	109	2	1	9	189	176	5	4	9	81	72	2	9	9	204	186
1	4	8	387	381	-3	9	8	169	174	3	1	9	257	246	-5	5	9	133	154	-2	10	9	152	148
2	4	8	335	336	0	9	8	111	107	4	1	9	72	71	-4	5	9	137	128	0	10	9	133	149
3	4	8	76	83	3	9	8	175	179	5	1	9	65	42	-3	5	9	111	116	2	10	9	150	141
4	4	8	177	181	4	9	8	102	109	-5	2	9	107	101	-2	5	9	160	184	-2	11	9	216	203
5	4	8	63	68	-5	10	8	73	71	-4	2	9	102	101	-1	5	9	142	103	0	11	9	249	263
-5	5	8	121	111	-3	10	8	222	209	-3	2	9	72	74	0	5	9	67	26	2	11	9	209	197
-4	5	8	150	153	0	10	8	181	143	-2	2	9	98	97	1	5	9	122	124	5	11	9	45	67
-3	5	8	94	95	3	10	8	226	208	-1	2	9	347	337	2	5	9	167	189	0	12	9	163	152
-2	5	8	182	189	5	10	8	78	70	0	2	9	205	193	3	5	9	114	122	-2	13	9	140	143
-1	5	8	259	277	0	11	8	99	91	1	2	9	356	331	4	5	9	132	131	0	13	9	194	201
0	5	8	232	226	-5	12	8	82	82	2	2	9	100	100	5	5	9	145	154	2	13	9	137	139
1	5	8	280	271	-3	12	8	127	133	3	2	9	78	81	-4	6	9	103	111	-2	14	9	116	120
2	5	8	191	183	3	12	8	126	131	4	2	9	99	103	-3	6	9	106	103	0	14	9	106	109
3	5	8	99	98	5	12	8	56	83	5	2	9	110	98	-2	6	9	114	116	0	17	9	97	89
4	5	8	155	153	-3	13	8	135	128	-5	3	9	148	132	-1	6	9	140	121	0	0	10	139	127
5	5	8	112	114	3	13	8	131	125	-4	3	9	101	127	0	6	9	174	153	1	0	10	492	458
-2	6	8	291	291	-3	14	8	109	105	-3	3	9	167	160	1	6	9	141	120	2	0	10	106	113
-1	6	8	449	417	3	14	8	99	106	-2	3	9	175	163	3	6	9	102	99	4	0	10	275	245

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR HERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-4	1	10	142	124	2	4	10	165	156	0	10	10	113	90	3	2	11	114	108	2	7	11	187	190
-3	1	10	71	77	3	4	10	170	172	1	10	10	187	207	4	2	11	124	128	3	7	11	161	172
-2	1	10	112	122	4	4	10	83	89	3	10	10	153	146	-4	3	11	166	157	4	7	11	95	94
0	1	10	104	95	5	4	10	74	82	-3	11	10	108	98	-3	3	11	218	224	5	7	11	70	67
2	1	10	115	119	-4	5	10	79	78	3	11	10	111	97	-2	3	11	113	119	-3	8	11	73	73
3	1	10	74	75	-3	5	10	83	75	-5	12	10	80	88	-1	3	11	181	202	-2	8	11	97	114
4	1	10	149	125	-2	5	10	197	215	-3	12	10	139	150	1	3	11	180	201	0	8	11	152	138
-4	2	10	263	252	-1	5	10	111	93	3	12	10	130	147	3	3	11	219	226	-5	9	11	67	79
-3	2	10	150	150	0	5	10	82	58	5	12	10	63	88	4	3	11	165	162	-3	9	11	91	90
-2	2	10	142	141	2	5	10	201	214	-3	13	10	91	92	-5	4	11	127	137	-2	9	11	138	122
-1	2	10	171	163	3	5	10	82	80	0	13	10	114	123	-3	4	11	69	72	0	9	11	108	107
0	2	10	94	75	4	5	10	80	75	0	14	10	92	88	-1	4	11	178	164	2	9	11	143	129
1	2	10	163	169	-5	6	10	37	67	1	0	11	177	211	1	4	11	184	156	3	9	11	91	91
2	2	10	147	138	-3	6	10	74	78	3	0	11	226	236	4	4	11	71	70	5	9	11	72	76
3	2	10	149	154	-2	6	10	166	166	4	0	11	158	157	5	4	11	116	136	0	10	11	212	203
4	2	10	278	251	-1	6	10	250	281	-5	1	11	65	43	-5	5	11	102	99	-4	11	11	103	109
-5	3	10	65	60	0	6	10	526	522	-4	1	11	117	110	-4	5	11	155	165	4	11	11	113	107
-4	3	10	140	154	1	6	10	238	287	-3	1	11	235	250	-3	5	11	126	107	0	12	11	112	111
-3	3	10	80	81	2	6	10	171	167	-2	1	11	141	143	-2	5	11	143	146	-2	13	11	174	171
-2	3	10	123	128	5	6	10	55	62	-1	1	11	410	422	-1	5	11	188	187	0	13	11	128	149
-1	3	10	219	219	-3	7	10	109	98	0	1	11	302	258	0	5	11	81	86	2	13	11	163	163
0	3	10	173	164	-2	7	10	176	175	1	1	11	416	426	1	5	11	198	182	-3	14	11	77	68
1	3	10	220	215	2	7	10	181	174	2	1	11	141	146	2	5	11	140	140	0	14	11	93	59
2	3	10	115	119	3	7	10	105	104	3	1	11	242	257	3	5	11	129	113	0	16	11	63	38
3	3	10	72	76	-2	8	10	180	183	4	1	11	115	108	4	5	11	152	170	0	0	12	394	379
4	3	10	148	153	-1	8	10	363	388	5	1	11	53	49	5	5	11	100	100	3	0	12	174	176
5	3	10	63	63	0	8	10	109	104	-5	2	11	113	122	-2	6	11	104	112	4	0	12	106	93
-5	4	10	72	88	1	8	10	371	383	-4	2	11	120	125	0	6	11	111	104	-4	1	12	162	158
-4	4	10	86	81	2	8	10	188	185	-3	2	11	99	100	-5	7	11	65	71	-2	1	12	138	126
-3	4	10	175	170	-3	9	10	140	136	-2	2	11	128	120	-4	7	11	104	91	-1	1	12	211	224
-2	4	10	146	143	0	9	10	77	78	-1	2	11	162	164	-3	7	11	151	165	0	1	12	280	271
-1	4	10	201	193	3	9	10	142	140	0	2	11	344	316	-2	7	11	186	189	1	1	12	219	226
0	4	10	297	326	-3	10	10	151	146	1	2	11	164	167	-1	7	11	150	138	2	1	12	137	125
1	4	10	201	197	-1	10	10	177	212	2	2	11	121	116	1	7	11	129	145	4	1	12	166	156

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR HERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-4	2	12	95	110	0	7	12	87	95	4	2	13	108	106	-5	8	13	38	54	0	3	14	352	335
-3	2	12	131	137	1	7	12	253	292	-5	3	13	75	63	-3	8	13	105	101	2	3	14	120	131
-2	2	12	142	167	4	7	12	96	98	-3	3	13	316	325	-2	8	13	150	144	3	3	14	181	160
-1	2	12	152	141	-5	8	12	35	65	0	3	13	289	264	0	8	13	91	90	-4	4	14	130	137
0	2	12	257	288	-3	8	12	125	106	3	3	13	318	324	2	8	13	143	136	-2	4	14	194	201
1	2	12	146	147	-2	8	12	151	149	4	3	13	79	69	3	8	13	97	103	-1	4	14	166	168
2	2	12	145	170	2	8	12	156	147	5	3	13	56	70	-4	9	13	99	109	1	4	14	175	162
3	2	12	138	140	3	8	12	120	99	-5	4	13	85	92	-2	9	13	212	193	2	4	14	204	212
4	2	12	93	113	5	8	12	55	62	-4	4	13	182	186	-1	9	13	177	166	4	4	14	140	128
-4	3	12	161	141	-5	10	12	87	98	-3	4	13	132	138	1	9	13	178	171	5	4	14	70	59
-2	3	12	97	106	0	10	12	153	160	-2	4	13	134	129	2	9	13	217	197	0	5	14	221	225
-1	3	12	158	155	5	10	12	85	100	0	4	13	343	337	4	9	13	114	107	-5	6	14	52	61
0	3	12	162	128	-3	11	12	123	110	1	4	13	119	117	0	10	13	155	170	-4	6	14	100	89
1	3	12	163	157	3	11	12	112	108	2	4	13	135	130	-2	11	13	141	135	-3	6	14	112	105
4	3	12	155	145	0	12	12	121	117	3	4	13	138	146	0	11	13	150	156	3	6	14	109	102
-5	4	12	63	70	-3	13	12	104	100	4	4	13	171	191	2	11	13	130	129	4	6	14	79	95
-3	4	12	85	93	3	13	12	104	99	5	4	13	99	93	0	13	13	97	97	5	6	14	35	62
-2	4	12	136	155	2	0	13	152	153	-4	5	13	101	106	0	14	13	105	102	-3	7	14	117	95
0	4	12	392	387	3	0	13	123	90	-3	5	13	138	149	0	0	14	394	380	3	7	14	103	95
2	4	12	147	158	4	0	13	80	74	0	5	13	97	107	3	0	14	191	177	-3	8	14	113	103
3	4	12	93	101	-5	1	13	87	89	3	5	13	147	156	4	0	14	106	108	-2	8	14	123	112
5	4	12	67	69	-3	1	13	148	148	4	5	13	108	113	5	0	14	103	111	3	8	14	118	93
-2	5	12	127	139	-2	1	13	118	135	-2	6	13	165	174	-3	1	14	127	129	0	9	14	85	73
-1	5	12	209	216	-1	1	13	218	265	0	6	13	109	98	-2	1	14	133	118	5	9	14	66	65
0	5	12	453	452	0	1	13	76	94	2	6	13	169	174	-1	1	14	232	202	-3	11	14	78	74
1	5	12	210	218	1	1	13	238	256	-5	7	13	48	59	1	1	14	230	204	0	11	14	113	105
-3	6	12	155	139	2	1	13	122	136	-4	7	13	91	99	2	1	14	136	118	0	12	14	155	150
-1	6	12	211	215	3	1	13	131	135	-3	7	13	86	79	3	1	14	125	128	0	13	14	107	86
0	6	12	152	201	5	1	13	96	96	-2	7	13	175	167	-4	2	14	87	94	0	15	14	94	75
1	6	12	217	211	-5	2	13	47	55	0	7	13	129	133	-2	2	14	159	136	0	16	14	79	30
3	6	12	142	131	-4	2	13	95	106	2	7	13	181	172	0	2	14	377	389	1	0	15	227	230
-4	7	12	91	101	-3	2	13	184	181	3	7	13	90	81	2	2	14	159	140	-5	1	15	78	74
-2	7	12	120	140	0	2	13	115	129	4	7	13	100	94	-3	3	14	173	155	-3	1	15	132	123
-1	7	12	258	295	3	2	13	189	188	5	7	13	57	58	-2	3	14	126	133	2	1	15	113	122

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR MERGE SPLIT LEVELS

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
3	1	15	135	129	-2	7	15	179	167	-2	3	16	183	176	3	1	17	124	133	3	2	18	112	107
5	1	15	78	78	-1	7	15	236	243	0	3	16	286	285	5	1	17	57	59	-3	3	18	153	143
-5	2	15	46	52	0	7	15	172	167	2	3	16	185	184	2	3	17	125	111	0	3	18	222	223
-3	2	15	119	117	1	7	15	244	240	4	3	16	69	74	-5	4	17	45	58	3	3	18	157	145
0	2	15	151	170	2	7	15	184	176	5	3	16	48	57	-2	4	17	214	187	-2	4	18	226	235
3	2	15	119	116	-2	8	15	156	136	-5	4	16	61	53	2	4	17	214	188	2	4	18	217	201
-4	3	15	90	79	2	8	15	166	143	-3	4	16	194	179	5	4	17	58	59	-3	5	18	48	62
-3	3	15	115	95	4	8	15	76	75	3	4	16	202	182	0	5	17	94	93	-3	8	18	121	105
-2	3	15	191	173	-2	9	15	147	143	5	4	16	51	54	-3	6	17	112	110	3	8	18	113	103
2	3	15	198	179	2	9	15	144	141	-3	5	16	145	124	-2	6	17	131	118	2	0	19	143	122
3	3	15	114	99	0	17	15	71	75	0	5	16	110	124	2	6	17	139	123	3	0	19	112	103
4	3	15	79	80	0	0	16	494	493	3	5	16	156	127	3	6	17	114	111	0	4	19	116	83
-3	4	15	142	136	2	0	16	300	296	-5	6	16	76	82	0	7	17	108	110	1	4	19	152	204
-2	4	15	156	133	3	0	16	250	229	-2	6	16	110	116	0	8	17	104	106	0	5	19	168	174
0	4	15	183	176	-5	1	16	60	71	2	6	16	108	110	2	9	17	125	114	0	7	19	123	115
2	4	15	144	128	-3	1	16	101	90	5	6	16	66	81	-4	10	17	69	60	0	0	20	284	291
3	4	15	140	135	0	1	16	108	110	-2	7	16	159	156	0	11	17	136	111	0	1	20	117	123
-4	5	15	96	103	3	1	16	103	93	2	7	16	162	155	0	0	18	273	219	0	3	20	123	111
-3	5	15	137	119	5	1	16	74	70	-4	8	16	65	80	-5	1	18	57	60	-3	5	20	83	72
-1	5	15	146	180	-4	2	16	77	78	4	8	16	83	78	-2	1	18	205	192	3	5	20	83	74
0	5	15	174	137	-3	2	16	100	88	-3	14	16	49	63	0	1	18	104	107	3	10	20	53	53
1	5	15	174	180	-2	2	16	188	181	3	14	16	49	63	2	1	18	209	198	-3	11	20	46	46
3	5	15	145	124	0	2	16	208	225	3	0	17	209	201	5	1	18	56	60	0	3	21	100	83
4	5	15	107	102	2	2	16	197	191	-5	1	17	46	59	-3	2	18	111	108	0	5	21	91	93
-3	6	15	122	120	3	2	16	105	86	-3	1	17	135	142	-2	2	18	128	129	3	5	22	55	69
-2	6	15	120	113	4	2	16	82	69	-2	1	17	135	117	0	2	18	150	148	0	8	23	94	87
3	6	15	123	123	-5	3	16	49	59	2	1	17	134	118	2	2	18	122	127					

APPENDIX C

TABLE XVII

List of Structure Factors for Seco penicillin E.B. 976

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	0	0	650	774	7	3	0	84	91	6	7	0	63	73	6	0	1	198	212	3	2	1	338	340
3	0	0	126	120	8	3	0	206	201	7	7	0	71	58	7	0	1	197	185	4	2	1	29	44
4	0	0	194	186	10	3	0	83	81	8	7	0	56	50	10	0	1	141	123	5	2	1	120	139
5	0	0	94	88	11	3	0	44	36	9	7	0	28	29	-11	1	1	41	41	6	2	1	77	92
6	0	0	231	226	2	4	0	430	371	10	7	0	36	33	-10	1	1	112	106	7	2	1	106	115
7	0	0	221	230	3	4	0	133	132	1	8	0	85	86	-9	1	1	95	85	8	2	1	129	132
8	0	0	139	126	4	4	0	331	259	2	8	0	139	155	-8	1	1	69	72	9	2	1	118	107
10	0	0	70	55	5	4	0	243	221	3	8	0	112	117	-7	1	1	136	131	10	2	1	69	60
11	0	0	90	30	6	4	0	91	76	4	8	0	62	65	-6	1	1	105	102	11	2	1	35	41
2	1	0	211	207	7	4	0	154	149	5	8	0	120	120	-5	1	1	537	560	-11	3	1	36	42
3	1	0	568	564	8	4	0	63	68	6	8	0	87	77	-4	1	1	184	197	-10	3	1	34	39
4	1	0	448	431	9	4	0	114	132	7	8	0	59	52	-3	1	1	267	278	-9	3	1	44	42
5	1	0	67	70	10	4	0	25	36	8	8	0	23	26	-2	1	1	676	655	-8	3	1	80	73
6	1	0	100	90	11	4	0	44	49	9	8	0	37	31	2	1	1	281	276	-7	3	1	196	184
7	1	0	72	78	2	5	0	176	157	1	9	0	101	101	3	1	1	43	32	-6	3	1	139	147
8	1	0	98	83	3	5	0	125	134	2	9	0	106	107	4	1	1	100	102	-5	3	1	52	60
9	1	0	124	119	4	5	0	164	177	3	9	0	75	55	5	1	1	241	230	-4	3	1	108	103
10	1	0	124	131	5	5	0	48	40	4	9	0	79	83	6	1	1	58	50	-3	3	1	213	186
11	1	0	49	40	6	5	0	87	86	5	9	0	55	47	7	1	1	52	63	-2	3	1	110	102
2	2	0	641	695	8	5	0	90	94	6	9	0	81	86	8	1	1	82	55	2	3	1	450	463
3	2	0	165	142	10	5	0	57	53	7	9	0	24	25	9	1	1	48	45	3	3	1	275	238
4	2	0	251	262	2	6	0	235	239	8	9	0	71	67	10	1	1	39	45	4	3	1	302	321
5	2	0	250	248	3	6	0	141	147	-11	0	1	53	52	11	1	1	68	70	5	3	1	232	223
6	2	0	134	142	4	6	0	69	65	-10	0	1	51	33	-11	2	1	32	34	6	3	1	142	146
7	2	0	137	128	5	6	0	38	45	-9	0	1	42	42	-10	2	1	46	39	7	3	1	231	249
8	2	0	152	155	6	6	0	130	117	-8	0	1	66	55	-9	2	1	67	74	8	3	1	26	25
9	2	0	159	158	7	6	0	70	76	-7	0	1	74	76	-8	2	1	47	47	9	3	1	37	34
10	2	0	84	93	8	6	0	64	66	-5	0	1	211	181	-7	2	1	47	50	10	3	1	66	64
11	2	0	33	35	9	6	0	57	54	-4	0	1	212	224	-6	2	1	231	227	-9	4	1	92	95
2	3	0	316	308	3	7	0	209	196	-3	0	1	184	176	-5	2	1	147	145	-8	4	1	143	148
3	3	0	184	168	2	7	0	232	191	-2	0	1	441	457	-4	2	1	115	113	-7	4	1	71	79
4	3	0	287	264	3	7	0	204	166	2	0	1	561	596	-3	2	1	72	73	-6	4	1	59	65
5	3	0	132	121	4	7	0	37	35	3	0	1	173	145	-2	2	1	227	208	-5	4	1	39	34
6	3	0	176	157	5	7	0	62	56	4	0	1	32	46	2	2	1	131	100	-4	4	1	62	67

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-3	4	1	200	172	-3	6	1	132	142	-4	8	1	78	81	-3	0	2	302	345	-6	2	2	248	260
-2	4	1	252	228	-2	6	1	164	176	-3	8	1	39	41	-2	0	2	313	347	-5	2	2	68	71
2	4	1	131	128	1	6	1	141	139	-1	8	1	129	125	1	0	2	390	451	-4	2	2	570	518
3	4	1	666	550	2	6	1	108	118	1	8	1	93	87	2	0	2	221	180	-3	2	2	362	330
4	4	1	251	219	3	6	1	210	204	2	8	1	81	55	3	0	2	149	125	-2	2	2	51	49
5	4	1	41	34	4	6	1	83	86	3	8	1	209	196	5	0	2	344	341	1	2	2	871	941
6	4	1	86	84	5	6	1	44	44	4	8	1	114	107	6	0	2	220	202	2	2	2	137	148
7	4	1	140	152	6	6	1	59	48	5	8	1	38	36	7	0	2	49	46	3	2	2	172	182
8	4	1	107	113	7	6	1	64	60	6	8	1	45	41	8	0	2	105	77	4	2	2	469	440
9	4	1	55	64	8	6	1	59	58	7	8	1	98	96	9	0	2	102	102	5	2	2	129	113
10	4	1	30	35	9	6	1	34	31	8	8	1	38	34	11	0	2	66	73	6	2	2	228	215
-10	5	1	45	44	10	6	1	48	49	9	8	1	49	43	-9	1	2	81	89	7	2	2	208	225
-9	5	1	25	22	-10	7	1	37	36	-9	9	1	44	39	-8	1	2	141	139	8	2	2	83	41
-8	5	1	83	84	-9	7	1	68	68	-8	9	1	41	36	-7	1	2	194	199	9	2	2	104	103
-7	5	1	54	40	-8	7	1	96	90	-7	9	1	59	60	-6	1	2	87	84	10	2	2	86	91
-6	5	1	184	192	-7	7	1	134	132	-6	9	1	51	55	-5	1	2	198	185	-10	3	2	38	27
-5	5	1	36	47	-6	7	1	65	70	-5	9	1	103	100	-4	1	2	272	267	-8	3	2	55	60
-4	5	1	183	165	-5	7	1	132	123	-4	9	1	158	139	-3	1	2	568	569	-7	3	2	171	184
-3	5	1	52	58	-3	7	1	178	177	-3	9	1	90	86	-2	1	2	523	527	-6	3	2	97	104
-2	5	1	287	265	-2	7	1	67	56	-2	9	1	108	84	1	1	2	706	704	-5	3	2	233	225
2	5	1	279	240	-1	7	1	179	168	-1	9	1	124	120	2	1	2	739	738	-4	3	2	205	185
3	5	1	117	130	1	7	1	247	198	1	9	1	112	116	3	1	2	144	133	-3	3	2	328	342
4	5	1	104	99	3	7	1	123	121	2	9	1	140	162	4	1	2	364	358	-2	3	2	323	326
5	5	1	110	88	4	7	1	66	52	3	9	1	61	72	5	1	2	211	193	-1	3	2	365	373
6	5	1	27	34	5	7	1	84	93	4	9	1	63	58	6	1	2	105	98	1	3	2	342	357
8	5	1	106	98	6	7	1	29	21	5	9	1	88	85	7	1	2	200	180	2	3	2	236	187
9	5	1	82	35	7	7	1	93	103	6	9	1	53	48	8	1	2	112	119	3	3	2	476	455
10	5	1	29	28	8	7	1	55	60	7	9	1	42	33	10	1	2	74	70	4	3	2	290	283
-10	6	1	32	27	9	7	1	27	25	-10	0	2	67	72	11	1	2	37	35	5	3	2	205	185
-9	6	1	42	33	-9	8	1	31	23	-9	0	2	97	83	-11	2	2	78	90	6	3	2	64	81
-7	6	1	92	80	-8	8	1	90	87	-8	0	2	93	85	-10	2	2	53	55	7	3	2	59	53
-6	6	1	82	88	-7	8	1	45	49	-7	0	2	80	82	-9	2	2	44	60	8	3	2	41	43
-5	6	1	173	184	-6	8	1	135	145	-6	0	2	260	257	-8	2	2	133	143	9	3	2	96	84
-4	6	1	65	40	-5	8	1	150	141	-5	0	2	109	85	-7	2	2	86	89	10	3	2	35	32

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
11	3	2	48	51	2	5	2	258	249	-4	7	2	205	189	-9	9	2	29	34	9	0	3	101	89
-11	4	2	49	53	3	5	2	77	60	-3	7	2	165	154	-8	9	2	42	41	-11	1	3	36	28
-9	4	2	73	68	4	5	2	204	246	-2	7	2	172	171	-7	9	2	49	47	-9	1	3	101	98
-8	4	2	85	92	5	5	2	67	67	-1	7	2	93	72	-6	9	2	50	50	-8	1	3	83	77
-7	4	2	65	68	6	5	2	93	111	0	7	2	166	158	-5	9	2	56	68	-7	1	3	44	34
-6	4	2	40	42	7	5	2	110	110	1	7	2	62	58	-4	9	2	122	107	-6	1	3	111	86
-5	4	2	56	45	8	5	2	76	76	2	7	2	118	83	-3	9	2	253	217	-5	1	3	66	65
-4	4	2	335	309	9	5	2	48	50	3	7	2	110	100	-2	9	2	145	152	-4	1	3	251	249
-3	4	2	325	302	-10	6	2	50	50	4	7	2	180	165	-1	9	2	79	66	-3	1	3	64	71
-2	4	2	221	184	-9	6	2	45	39	5	7	2	120	113	0	9	2	106	95	-2	1	3	532	564
-1	4	2	258	223	-8	6	2	64	65	6	7	2	97	106	1	9	2	171	161	-1	1	3	583	582
1	4	2	416	337	-7	6	2	70	70	7	7	2	37	36	2	9	2	185	183	0	1	3	191	261
2	4	2	327	277	-6	6	2	224	232	8	7	2	24	19	3	9	2	100	86	1	1	3	507	565
3	4	2	613	533	-5	6	2	204	201	9	7	2	25	25	4	9	2	98	97	2	1	3	109	81
4	4	2	213	222	-4	6	2	150	158	10	7	2	39	37	5	9	2	33	30	3	1	3	496	516
5	4	2	177	163	-3	6	2	152	148	-9	8	2	39	40	7	9	2	65	69	4	1	3	107	109
6	4	2	111	113	-2	6	2	187	188	-8	8	2	40	43	8	9	2	39	39	5	1	3	40	48
7	4	2	57	64	-1	6	2	25	37	-7	8	2	56	60	-10	0	3	97	89	6	1	3	124	121
8	4	2	57	65	0	6	2	255	258	-6	8	2	80	67	-9	0	3	75	64	7	1	3	208	226
9	4	2	34	25	1	6	2	128	132	-5	8	2	164	156	-8	0	3	73	69	8	1	3	47	59
10	4	2	63	61	2	6	2	76	79	-4	8	2	181	190	-7	0	3	118	106	9	1	3	51	33
11	4	2	18	14	3	6	2	276	272	-3	8	2	177	164	-6	0	3	46	32	10	1	3	50	46
-10	5	2	33	32	4	6	2	91	76	-2	8	2	136	138	-5	0	3	69	35	11	1	3	44	44
-9	5	2	27	29	5	6	2	147	137	-1	8	2	52	68	-4	0	3	32	31	-10	2	3	63	67
-8	5	2	86	79	6	6	2	152	166	0	8	2	147	136	-2	0	3	296	290	-9	2	3	42	30
-7	5	2	124	130	7	6	2	104	116	1	8	2	24	32	-1	0	3	317	326	-8	2	3	42	47
-6	5	2	99	93	8	6	2	39	40	2	8	2	134	124	0	0	3	812	841	-7	2	3	101	105
-5	5	2	125	131	9	6	2	28	29	3	8	2	207	197	1	0	3	119	145	-6	2	3	138	129
-4	5	2	82	84	-10	7	2	70	68	4	8	2	56	48	2	0	3	409	396	-5	2	3	231	208
-3	5	2	214	224	-9	7	2	75	70	5	8	2	53	37	3	0	3	177	192	-4	2	3	73	87
-2	5	2	80	73	-8	7	2	70	74	6	8	2	29	23	4	0	3	83	103	-3	2	3	260	250
-1	5	2	163	167	-7	7	2	103	116	7	8	2	51	48	5	0	3	141	135	-1	2	3	705	679
0	5	2	36	29	-6	7	2	78	87	8	8	2	57	54	6	0	3	145	148	0	2	3	609	643
1	5	2	194	176	-5	7	2	84	79	9	8	2	28	23	8	0	3	40	36	1	2	3	489	482

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	2	3	241	242	-7	4	3	94	78	8	5	3	66	65	2	7	3	220	207	0	9	3	146	147
3	2	3	50	65	-6	4	3	75	72	9	5	3	27	24	3	7	3	139	125	1	9	3	110	87
4	2	3	167	165	-5	4	3	195	185	10	5	3	28	24	4	7	3	103	146	2	9	3	27	16
5	2	3	64	64	-4	4	3	220	227	-10	6	3	28	25	5	7	3	139	155	3	9	3	140	131
6	2	3	140	153	-3	4	3	111	114	-9	6	3	36	34	6	7	3	170	174	4	9	3	93	106
7	2	3	97	108	-2	4	3	326	303	-8	6	3	120	126	7	7	3	77	80	5	9	3	58	52
8	2	3	36	44	-1	4	3	144	150	-7	6	3	99	112	8	7	3	36	37	7	9	3	50	48
9	2	3	48	53	1	4	3	335	295	-6	6	3	100	97	9	7	3	46	52	8	9	3	17	22
10	2	3	45	38	2	4	3	41	40	-5	6	3	134	141	-9	8	3	65	66	-11	0	4	74	68
11	2	3	59	70	3	4	3	159	130	-4	6	3	206	199	-8	8	3	96	91	-9	0	4	82	85
-9	3	3	59	63	4	4	3	229	212	-3	6	3	74	71	-6	8	3	94	99	-8	0	4	147	128
-8	3	3	100	93	5	4	3	52	59	-2	6	3	179	188	-5	8	3	177	166	-6	0	4	86	71
-7	3	3	54	57	6	4	3	129	130	-1	6	3	118	143	-4	8	3	144	131	-5	0	4	172	158
-6	3	3	162	152	7	4	3	85	90	0	6	3	327	348	-3	8	3	84	79	-4	0	4	264	291
-5	3	3	232	228	8	4	3	54	59	1	6	3	131	127	-2	8	3	189	198	-2	0	4	725	839
-4	3	3	403	389	9	4	3	65	77	2	6	3	68	63	-1	8	3	112	110	-1	0	4	659	802
-3	3	3	119	118	10	4	3	25	32	3	6	3	47	46	0	8	3	73	72	0	0	4	357	361
-2	3	3	180	166	-9	5	3	74	69	4	6	3	335	380	1	8	3	196	222	1	0	4	337	375
-1	3	3	742	732	-8	5	3	81	93	5	6	3	218	221	2	8	3	108	105	3	0	4	372	382
1	3	3	366	338	-7	5	3	78	87	6	6	3	79	74	3	8	3	227	228	4	0	4	318	326
2	3	3	348	301	-6	5	3	208	218	7	6	3	40	35	4	8	3	106	90	5	0	4	151	137
3	3	3	246	222	-5	5	3	170	162	8	6	3	85	87	5	8	3	64	60	6	0	4	109	87
4	3	3	84	69	-4	5	3	133	123	9	6	3	35	34	6	8	3	91	103	7	0	4	61	59
5	3	3	165	179	-3	5	3	139	142	10	6	3	50	55	7	8	3	68	62	8	0	4	70	79
6	3	3	52	44	-2	5	3	67	87	-10	7	3	40	43	8	8	3	46	40	9	0	4	60	52
7	3	3	52	44	-1	5	3	523	453	-9	7	3	79	83	9	8	3	82	69	10	0	4	56	65
8	3	3	78	83	0	5	3	321	301	-7	7	3	47	50	-9	9	3	28	31	-11	1	4	92	94
9	3	3	68	63	1	5	3	207	196	-6	7	3	120	127	-7	9	3	80	73	-10	1	4	70	72
10	3	3	77	86	2	5	3	47	45	-5	7	3	169	153	-6	9	3	53	44	-9	1	4	130	114
11	3	3	27	31	3	5	3	347	326	-3	7	3	133	104	-5	9	3	56	62	-7	1	4	247	246
-11	4	3	68	60	4	5	3	91	111	-2	7	3	194	187	-4	9	3	138	139	-6	1	4	68	82
-10	4	3	34	34	5	5	3	192	200	-1	7	3	55	48	-3	9	3	200	204	-5	1	4	63	75
-9	4	3	33	35	6	5	3	65	68	0	7	3	93	92	-2	9	3	86	90	-4	1	4	238	223
-8	4	3	41	33	7	5	3	92	94	1	7	3	125	115	-1	9	3	82	72	-3	1	4	244	262

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-2	1	4	473	490	-9	3	4	65	57	3	4	4	98	92	-5	6	4	125	124	9	7	4	54	52
-1	1	4	339	372	-8	3	4	123	120	4	4	4	125	128	-4	6	4	143	162	-9	8	4	30	40
0	1	4	306	314	-7	3	4	53	43	5	4	4	58	46	-3	6	4	182	179	-8	8	4	53	49
1	1	4	348	341	-6	3	4	260	260	6	4	4	111	95	-2	6	4	104	109	-7	8	4	52	55
2	1	4	161	149	-5	3	4	82	71	7	4	4	69	63	-1	6	4	126	121	-6	8	4	60	49
3	1	4	199	203	-4	3	4	90	93	8	4	4	94	100	0	6	4	223	220	-5	8	4	169	164
4	1	4	217	213	-3	3	4	335	305	9	4	4	44	39	1	6	4	121	115	-4	8	4	55	59
5	1	4	111	111	-2	3	4	203	202	10	4	4	26	32	2	6	4	175	193	-3	8	4	220	224
6	1	4	72	82	-1	3	4	120	103	-10	5	4	25	24	3	6	4	70	76	-2	8	4	74	71
7	1	4	55	67	0	3	4	154	156	-9	5	4	91	90	4	6	4	151	142	-1	8	4	143	127
8	1	4	53	45	1	3	4	349	333	-8	5	4	98	95	5	6	4	147	140	0	8	4	86	82
-9	1	4	51	63	2	3	4	215	223	-7	5	4	109	106	6	6	4	139	134	1	8	4	89	99
-10	2	4	77	78	3	3	4	226	200	-6	5	4	151	156	7	6	4	45	32	2	8	4	97	126
-9	2	4	94	93	4	3	4	72	77	-5	5	4	88	83	8	6	4	45	43	3	8	4	98	108
-8	2	4	74	65	5	3	4	38	38	-4	5	4	212	227	9	6	4	94	89	4	8	4	181	210
-7	2	4	168	166	6	3	4	191	194	-3	5	4	184	187	-10	7	4	36	38	5	8	4	114	121
-6	2	4	168	155	7	3	4	209	204	-2	5	4	350	352	-9	7	4	77	85	6	8	4	34	24
-5	2	4	48	59	8	3	4	59	53	-1	5	4	467	434	-8	7	4	62	69	7	8	4	115	117
-4	2	4	332	303	9	3	4	65	71	0	5	4	454	401	-7	7	4	78	72	8	8	4	61	60
-3	2	4	412	411	10	3	4	43	42	1	5	4	355	344	-6	7	4	87	90	-9	9	4	54	51
-2	2	4	361	339	-11	4	4	20	15	2	5	4	192	181	-5	7	4	53	56	-8	9	4	64	65
-1	2	4	699	693	-10	4	4	105	110	3	5	4	99	104	-4	7	4	37	30	-7	9	4	23	25
0	2	4	736	736	-9	4	4	43	46	4	5	4	249	251	-3	7	4	136	139	-6	9	4	76	87
1	2	4	297	289	-8	4	4	83	87	5	5	4	236	242	-2	7	4	106	99	-5	9	4	143	141
2	2	4	331	321	-7	4	4	91	85	6	5	4	41	43	-1	7	4	191	189	-4	9	4	135	143
3	2	4	141	133	-6	4	4	109	123	7	5	4	69	51	0	7	4	141	147	-3	9	4	149	152
4	2	4	239	226	-5	4	4	213	213	8	5	4	86	84	1	7	4	110	105	-2	9	4	219	219
5	2	4	55	58	-4	4	4	111	105	9	5	4	27	20	2	7	4	56	46	-1	9	4	47	41
6	2	4	69	62	-3	4	4	81	82	10	5	4	81	79	3	7	4	236	229	0	9	4	124	116
7	2	4	200	209	-2	4	4	131	109	-10	6	4	51	47	4	7	4	115	113	1	9	4	59	43
8	2	4	48	37	-1	4	4	484	614	-9	6	4	29	30	5	7	4	132	139	2	9	4	144	130
11	2	4	36	43	0	4	4	98	103	-8	6	4	35	26	6	7	4	82	88	3	9	4	91	114
-11	3	4	63	62	1	4	4	522	489	-7	6	4	69	56	7	7	4	100	96	4	9	4	40	36
-10	3	4	32	36	2	4	4	205	193	-6	6	4	183	199	8	7	4	84	88	5	9	4	43	44

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
6	9	4	52	46	6	1	5	93	110	-1	3	5	122	119	-5	5	5	138	130	-8	7	5	81	79
7	9	4	73	71	7	1	5	101	88	0	3	5	80	70	-4	5	5	167	180	-7	7	5	35	28
8	9	4	46	40	8	1	5	56	52	1	3	5	135	149	-3	5	5	136	136	-6	7	5	62	50
-8	0	5	28	35	10	1	5	65	62	2	3	5	414	400	-2	5	5	304	355	-5	7	5	58	55
-7	0	5	190	197	-11	2	5	63	63	3	3	5	179	167	-1	5	5	308	345	-4	7	5	144	135
-6	0	5	43	40	-10	2	5	85	80	4	3	5	157	154	0	5	5	283	282	-3	7	5	89	88
-5	0	5	35	21	-9	2	5	88	82	5	3	5	64	55	1	5	5	57	40	-2	7	5	93	77
-4	0	5	220	207	-8	2	5	59	56	6	3	5	111	106	2	5	5	145	131	-1	7	5	93	80
-3	0	5	305	324	-7	2	5	68	69	7	3	5	85	111	3	5	5	84	95	0	7	5	233	208
-2	0	5	317	359	-6	2	5	105	101	8	3	5	54	66	4	5	5	68	60	1	7	5	93	109
-1	0	5	466	554	-5	2	5	150	143	9	3	5	77	71	5	5	5	68	77	3	7	5	41	26
0	0	5	158	162	-4	2	5	208	195	-11	4	5	32	28	6	5	5	204	218	4	7	5	122	126
2	0	5	287	288	-3	2	5	178	182	-9	4	5	96	88	7	5	5	77	79	5	7	5	23	31
3	0	5	100	84	-2	2	5	249	215	-8	4	5	101	116	8	5	5	26	26	6	7	5	119	114
4	0	5	30	16	-1	2	5	241	239	-7	4	5	88	97	9	5	5	34	28	7	7	5	72	69
6	0	5	183	186	0	2	5	35	63	-6	4	5	92	101	-10	6	5	46	42	8	7	5	68	70
7	0	5	218	224	1	2	5	144	143	-5	4	5	296	286	-8	6	5	57	45	9	7	5	48	49
8	0	5	35	46	2	2	5	212	220	-3	4	5	241	204	-7	6	5	83	83	-9	8	5	62	63
9	0	5	74	64	3	2	5	163	167	-2	4	5	113	105	-6	6	5	121	114	-8	8	5	62	57
-11	1	5	95	89	5	2	5	69	66	-1	4	5	157	152	-5	6	5	123	141	-7	8	5	94	88
-9	1	5	113	117	6	2	5	147	143	0	4	5	462	420	-4	6	5	124	111	-6	8	5	29	20
-7	1	5	59	52	7	2	5	74	80	1	4	5	69	63	-3	6	5	106	99	-5	8	5	56	47
-6	1	5	167	174	8	2	5	94	87	2	4	5	139	130	-2	6	5	109	109	-4	8	5	58	47
-5	1	5	102	98	9	2	5	52	53	3	4	5	80	77	-1	6	5	144	140	-3	8	5	126	137
-4	1	5	55	44	10	2	5	26	29	4	4	5	103	82	0	6	5	76	74	-2	8	5	165	191
-3	1	5	403	413	-10	3	5	58	51	5	4	5	111	122	1	6	5	95	93	-1	8	5	85	86
-2	1	5	417	413	-9	3	5	88	81	6	4	5	184	196	2	6	5	93	109	0	8	5	122	131
-1	1	5	163	170	-8	3	5	50	45	7	4	5	90	106	3	6	5	145	144	1	8	5	60	26
0	1	5	283	304	-7	3	5	126	121	9	4	5	52	53	4	6	5	99	99	2	8	5	83	76
1	1	5	224	230	-6	3	5	102	98	10	4	5	39	40	5	6	5	63	56	3	8	5	55	50
2	1	5	320	332	-5	3	5	60	59	-10	5	5	48	36	6	6	5	84	86	4	8	5	128	147
3	1	5	62	54	-4	3	5	96	98	-9	5	5	83	74	7	6	5	132	126	5	8	5	82	84
4	1	5	145	144	-3	3	5	225	218	-8	5	5	69	62	8	6	5	68	64	7	8	5	51	47
5	1	5	107	103	-2	3	5	200	191	-6	5	5	159	204	-9	7	5	57	45	8	8	5	42	39

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-8	9	5	45	48	8	0	6	71	60	3	2	6	46	44	-7	4	6	61	76	7	5	6	75	75
-8	9	5	67	75	9	0	6	49	45	4	2	6	74	70	-6	4	6	109	102	8	5	6	82	83
-7	9	5	25	22	-10	1	6	117	109	5	2	6	236	247	-5	4	6	70	67	9	5	6	37	30
-6	9	5	87	81	-9	1	6	65	64	6	2	6	126	148	-4	4	6	251	255	-9	6	6	64	65
-5	9	5	49	52	-8	1	6	99	101	7	2	6	127	153	-3	4	6	96	106	-8	6	6	68	65
-4	9	5	23	12	-7	1	6	99	91	8	2	6	54	52	-2	4	6	108	89	-7	6	6	131	133
-3	9	5	184	165	-6	1	6	165	181	9	2	6	63	70	-1	4	6	259	259	-6	6	6	176	170
-2	9	5	85	90	-5	1	6	135	131	10	2	6	27	37	0	4	6	434	362	-5	6	6	131	128
-1	9	5	120	130	-4	1	6	286	270	-11	3	6	56	60	1	4	6	337	324	-4	6	6	204	208
0	9	5	126	128	-3	1	6	133	135	-10	3	6	39	25	2	4	6	340	341	-3	6	6	99	74
1	9	5	170	169	-2	1	6	415	421	-9	3	6	43	38	3	4	6	177	180	-2	6	6	98	108
2	9	5	55	56	-1	1	6	230	242	-8	3	6	218	225	4	4	6	92	87	-1	6	6	62	47
3	9	5	67	73	0	1	6	84	83	-7	3	6	114	116	5	4	6	31	23	0	6	6	248	236
4	9	5	69	67	1	1	6	259	265	-6	3	6	30	39	6	4	6	93	75	1	6	6	174	187
5	9	5	76	81	2	1	6	255	238	-5	3	6	107	98	7	4	6	145	163	2	6	6	246	234
6	9	5	32	33	3	1	6	187	165	-4	3	6	97	94	8	4	6	71	70	3	6	6	110	110
8	9	5	42	67	4	1	6	78	76	-3	3	6	147	137	9	4	6	33	29	4	6	6	67	73
-11	0	6	47	41	6	1	6	144	134	-2	3	6	162	144	-10	5	6	80	73	5	6	6	171	181
-10	0	6	65	58	7	1	6	51	39	-1	3	6	271	281	-9	5	6	43	43	6	6	6	64	64
-8	0	6	33	15	9	1	6	58	54	0	3	6	366	365	-8	5	6	83	87	7	6	6	104	106
-7	0	6	191	189	10	1	6	64	65	1	3	6	241	245	-7	5	6	180	178	8	6	6	65	60
-6	0	6	100	111	-10	2	6	31	33	2	3	6	173	157	-6	5	6	86	82	9	6	6	35	38
-5	0	6	37	37	-9	2	6	100	106	3	3	6	133	146	-5	5	6	109	103	-9	7	6	42	40
-4	0	6	155	127	-8	2	6	47	54	4	3	6	79	71	-4	5	6	51	44	-8	7	6	88	102
-3	0	6	352	401	-7	2	6	165	158	5	3	6	109	107	-3	5	6	392	389	-7	7	6	100	95
-2	0	6	160	122	-6	2	6	76	77	6	3	6	167	196	-2	5	6	66	57	-6	7	6	73	77
0	0	6	400	438	-5	2	6	145	140	7	3	6	22	21	-1	5	6	111	112	-5	7	6	46	58
1	0	6	347	376	-4	2	6	187	192	8	3	6	42	39	0	5	6	210	210	-4	7	6	113	122
2	0	6	205	192	-3	2	6	245	235	9	3	6	76	64	1	5	6	315	271	-3	7	6	85	95
3	0	6	153	146	-2	2	6	468	433	10	3	6	27	35	2	5	6	144	149	-2	7	6	103	98
4	0	6	116	105	-1	2	6	113	99	-11	4	6	60	66	3	5	6	122	109	-1	7	6	111	101
5	0	6	157	157	0	2	6	206	209	-10	4	6	33	36	4	5	6	101	101	0	7	6	37	34
6	0	6	121	106	1	2	6	248	217	-9	4	6	54	67	5	5	6	90	99	1	7	6	102	111
7	0	6	208	202	2	2	6	123	117	-8	4	6	135	132	6	5	6	46	42	2	7	6	98	100

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
3	7	6	121	131	6	9	6	59	57	2	1	7	182	179	-3	3	7	177	181	-9	5	7	44	38
4	7	6	100	150	7	9	6	26	23	3	1	7	261	269	-2	3	7	145	144	-8	5	7	111	102
5	7	6	36	60	-10	0	7	34	31	4	1	7	141	148	-1	3	7	206	204	-7	5	7	114	105
6	7	6	71	76	-9	0	7	139	137	5	1	7	191	195	0	3	7	91	87	-6	5	7	146	150
8	7	6	57	56	-7	0	7	59	68	6	1	7	66	62	1	3	7	75	84	-4	5	7	135	153
0	7	6	53	61	-6	0	7	129	117	8	1	7	66	71	2	3	7	278	292	-3	5	7	150	146
-9	8	6	76	75	-5	0	7	183	168	9	1	7	99	97	3	3	7	140	110	-2	5	7	52	40
-8	8	6	27	32	-4	0	7	196	189	-11	2	7	59	64	4	3	7	117	141	-1	5	7	161	159
-6	8	6	115	109	-3	0	7	319	302	-10	2	7	69	63	5	3	7	56	61	0	5	7	181	206
-5	8	6	49	61	-2	0	7	114	97	-9	2	7	71	65	6	3	7	83	89	1	5	7	84	79
-4	8	6	115	121	-1	0	7	193	194	-7	2	7	128	137	7	3	7	75	82	2	5	7	58	78
-3	8	6	51	44	0	0	7	200	206	-6	2	7	198	202	8	3	7	46	37	3	5	7	110	116
-2	8	6	130	190	1	0	7	141	147	-5	2	7	185	177	9	3	7	33	33	4	5	7	59	62
-1	8	6	120	120	2	0	7	109	108	-4	2	7	162	155	-10	4	7	40	43	5	5	7	37	39
0	8	6	76	79	3	0	7	130	128	-3	2	7	243	224	-9	4	7	38	42	6	5	7	93	93
1	8	6	185	134	4	0	7	92	99	-2	2	7	154	158	-8	4	7	133	136	7	5	7	45	39
2	8	6	170	162	5	0	7	142	138	-1	2	7	313	300	-7	4	7	88	106	9	5	7	35	27
3	8	6	89	86	6	0	7	205	217	0	2	7	208	221	-6	4	7	147	160	-10	6	7	46	45
4	8	6	81	80	7	0	7	68	59	1	2	7	253	265	-5	4	7	63	51	-9	6	7	32	32
5	8	6	93	89	8	0	7	43	14	2	2	7	133	117	-4	4	7	144	143	-8	6	7	93	86
8	8	6	47	43	9	0	7	69	61	3	2	7	232	223	-3	4	7	44	44	-6	6	7	177	167
-8	9	6	42	44	10	0	7	48	54	4	2	7	54	52	-2	4	7	119	108	-5	6	7	132	122
-7	9	6	41	15	-10	1	7	63	67	5	2	7	103	129	-1	4	7	145	130	-4	6	7	77	73
-6	9	6	48	52	-9	1	7	72	62	6	2	7	149	148	0	4	7	65	10	-3	6	7	90	61
-5	9	6	100	101	-8	1	7	84	79	7	2	7	66	69	1	4	7	225	226	-2	6	7	167	170
-4	9	6	69	62	-7	1	7	190	186	8	2	7	38	56	2	4	7	100	109	-1	6	7	83	66
-3	9	6	167	182	-6	1	7	43	35	10	2	7	41	49	3	4	7	185	207	0	6	7	113	105
-2	9	6	131	132	-5	1	7	263	281	-10	3	7	44	38	4	4	7	103	96	1	6	7	145	164
-1	9	6	41	53	-4	1	7	267	273	-9	3	7	35	25	5	4	7	28	10	2	6	7	102	104
0	9	6	124	121	-3	1	7	89	97	-8	3	7	82	96	6	4	7	71	60	3	6	7	146	152
1	9	6	215	219	-2	1	7	332	318	-7	3	7	148	144	7	4	7	64	60	4	6	7	84	69
2	9	6	108	111	-1	1	7	51	48	-6	3	7	207	213	8	4	7	53	77	5	6	7	29	34
4	9	6	59	52	0	1	7	287	272	-5	3	7	113	109	9	4	7	42	52	6	6	7	58	66
5	9	6	33	36	1	1	7	154	155	-4	3	7	37	27	-10	5	7	36	38	7	6	7	34	29

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
8	6	7	60	55	-5	9	7	79	74	-6	1	8	149	155	-8	3	8	36	39	8	4	8	33	23
0	6	7	23	21	-4	9	7	66	63	-5	1	8	170	171	-7	3	8	243	245	9	4	8	44	46
-9	7	7	52	44	-3	9	7	70	58	-4	1	8	141	138	-6	3	8	134	147	-10	5	8	35	32
-7	7	7	113	105	-2	9	7	124	137	-3	1	8	105	109	-5	3	8	135	165	-9	5	8	30	18
-6	7	7	60	61	-1	9	7	34	44	-2	1	8	134	140	-4	3	8	133	139	-7	5	8	64	57
-5	7	7	111	97	0	9	7	105	88	-1	1	8	202	182	-3	3	8	143	169	-6	5	8	99	101
-4	7	7	80	78	1	9	7	66	67	0	1	8	369	384	-2	3	8	63	72	-5	5	8	45	50
-3	7	7	124	123	2	9	7	81	98	1	1	8	330	334	-1	3	8	50	42	-4	5	8	183	196
-2	7	7	66	63	3	9	7	17	21	2	1	8	217	224	0	3	8	250	264	-3	5	8	43	49
-1	7	7	41	39	4	9	7	36	32	3	1	8	42	54	1	3	8	80	71	-2	5	8	165	182
1	7	7	59	42	5	9	7	50	57	4	1	8	55	38	2	3	8	97	114	-1	5	8	211	202
2	7	7	80	83	6	9	7	21	21	6	1	8	68	69	3	3	8	180	195	0	5	8	78	65
3	7	7	41	48	7	9	7	21	22	7	1	8	71	77	4	3	8	142	155	1	5	8	152	155
4	7	7	95	106	-11	0	8	73	81	-11	2	8	30	29	5	3	8	174	179	2	5	8	183	202
5	7	7	52	53	-10	0	8	37	29	-10	2	8	64	66	6	3	8	70	75	3	5	8	141	136
6	7	7	47	46	-8	0	8	102	95	-9	2	8	83	84	7	3	8	61	60	4	5	8	92	98
7	7	7	61	70	-7	0	8	101	85	-8	2	8	143	131	8	3	8	36	25	5	5	8	84	77
8	7	7	23	16	-6	0	8	126	129	-7	2	8	81	80	9	3	8	29	24	6	5	8	90	82
-9	8	7	25	28	-5	0	8	97	83	-6	2	8	129	143	-9	4	8	45	47	8	5	8	34	27
-8	8	7	78	61	-4	0	8	48	26	-5	2	8	134	128	-8	4	8	77	97	-10	6	8	31	33
-7	8	7	51	53	-3	0	8	159	140	-4	2	8	252	249	-6	4	8	229	216	-8	6	8	26	25
-6	8	7	72	60	-2	0	8	360	375	-3	2	8	142	137	-5	4	8	159	161	-7	6	8	73	78
-5	8	7	105	111	-1	0	8	147	156	-2	2	8	160	157	-4	4	8	53	57	-6	6	8	104	116
-4	8	7	52	51	0	0	8	166	172	-1	2	8	154	165	-3	4	8	134	148	-5	6	8	105	96
-3	8	7	23	24	2	0	8	141	128	0	2	8	152	142	-2	4	8	112	104	-4	6	8	67	72
-2	8	7	104	109	4	0	8	134	129	1	2	8	213	230	-1	4	8	191	188	-3	6	8	97	111
-1	8	7	171	160	5	0	8	57	44	2	2	8	71	81	0	4	8	144	134	-2	6	8	41	39
0	8	7	95	94	6	0	8	54	62	3	2	8	252	254	1	4	8	178	172	-1	6	8	122	116
1	8	7	44	39	9	0	8	71	67	4	2	8	110	95	2	4	8	136	127	0	6	8	20	15
2	8	7	104	97	-11	1	8	37	31	5	2	8	155	150	3	4	8	200	194	1	6	8	284	269
3	8	7	81	72	-10	1	8	39	26	6	2	8	110	119	4	4	8	91	90	2	6	8	107	103
7	8	7	21	22	-9	1	8	91	96	8	2	8	63	57	5	4	8	108	113	3	6	8	143	144
8	8	7	34	33	-8	1	8	85	82	-11	3	8	30	30	6	4	8	89	83	4	6	8	69	61
-7	0	7	51	40	-7	1	8	97	87	-10	3	8	64	67	7	4	8	48	41	5	6	8	103	105

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
7	6	8	67	64	-7	9	8	49	41	-3	1	9	158	148	-5	3	9	101	93	-9	5	9	25	25
8	6	8	69	67	-6	9	8	36	36	-2	1	9	164	156	-4	3	9	169	171	-7	5	9	58	59
-8	7	8	37	33	-5	9	8	69	73	-1	1	9	120	124	-3	3	9	139	138	-6	5	9	65	65
-7	7	8	94	83	-4	9	8	48	41	0	1	9	92	81	-2	3	9	146	165	-5	5	9	112	121
-6	7	8	79	68	-3	9	8	64	49	1	1	9	112	116	-1	3	9	118	117	-4	5	9	67	65
-5	7	8	85	89	-2	9	8	52	57	2	1	9	197	197	0	3	9	178	188	-3	5	9	98	99
-4	7	8	94	97	-1	9	8	82	68	3	1	9	95	82	1	3	9	134	130	-2	5	9	256	253
-3	7	8	196	202	0	9	8	98	107	4	1	9	80	78	2	3	9	39	34	-1	5	9	69	74
-2	7	8	140	145	1	9	8	48	48	5	1	9	101	112	3	3	9	108	104	0	5	9	35	28
-1	7	8	62	65	2	9	8	46	39	7	1	9	66	52	4	3	9	155	168	1	5	9	105	124
0	7	8	71	73	3	9	8	43	47	-10	2	9	35	25	5	3	9	146	158	2	5	9	137	146
1	7	8	140	141	4	9	8	50	55	-9	2	9	51	48	6	3	9	55	66	3	5	9	179	165
2	7	8	193	197	5	9	8	33	29	-8	2	9	47	52	7	3	9	29	28	4	5	9	84	78
3	7	8	79	79	6	9	8	33	35	-7	2	9	89	83	8	3	9	31	25	5	5	9	112	106
4	7	8	69	78	-11	0	9	41	40	-6	2	9	114	106	9	3	9	45	46	6	5	9	74	76
5	7	8	78	76	-10	0	9	91	88	-5	2	9	172	173	-10	4	9	31	32	7	5	9	47	43
7	7	8	49	51	-8	0	9	86	71	-4	2	9	50	46	-9	4	9	36	33	8	5	9	25	25
-9	8	8	29	27	-6	0	9	69	71	-3	2	9	161	174	-8	4	9	85	92	-10	6	9	40	51
-8	8	8	56	54	-5	0	9	237	252	-2	2	9	118	115	-7	4	9	106	124	-9	6	9	48	39
-7	8	8	61	50	-3	0	9	297	281	-1	2	9	101	115	-6	4	9	118	133	-8	6	9	43	43
-6	8	8	131	138	-2	0	9	119	104	0	2	9	165	162	-5	4	9	199	196	-7	6	9	121	117
-4	8	8	106	92	-1	0	9	179	199	1	2	9	80	79	-4	4	9	88	107	-6	6	9	98	106
-3	8	8	49	54	0	0	9	124	121	2	2	9	103	106	-3	4	9	109	116	-5	6	9	33	36
-2	8	8	92	84	1	0	9	123	126	3	2	9	91	98	-2	4	9	80	76	-4	6	9	162	169
-1	8	8	46	53	2	0	9	81	82	4	2	9	106	103	-1	4	9	101	109	-3	6	9	127	132
0	8	8	113	113	3	0	9	167	151	5	2	9	64	63	0	4	9	136	125	-2	6	9	52	48
1	8	8	103	106	5	0	9	83	95	6	2	9	170	172	1	4	9	61	60	-1	6	9	121	119
2	8	8	123	128	6	0	9	68	77	7	2	9	41	47	2	4	9	31	26	0	6	9	163	174
3	8	8	122	119	7	0	9	47	49	8	2	9	44	36	3	4	9	106	103	1	6	9	67	64
4	8	8	42	44	-8	1	9	67	70	-10	3	9	43	50	4	4	9	105	102	2	6	9	65	63
5	8	8	35	32	-7	1	9	107	97	-9	3	9	23	39	5	4	9	63	63	4	6	9	73	79
6	8	8	61	57	-6	1	9	135	126	-8	3	9	72	72	6	4	9	62	91	6	6	9	28	19
7	8	8	61	64	-5	1	9	60	63	-7	3	9	92	88	8	4	9	37	45	7	6	9	35	36
-8	0	9	19	18	-4	1	9	317	315	-6	3	9	155	156	-10	5	9	41	44	8	6	9	32	28

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-9	7	9	56	53	-2	9	9	110	114	3	1	10	120	115	2	3	10	41	30	2	5	10	29	25
-8	7	9	50	41	-1	9	9	56	58	4	1	10	51	49	3	3	10	56	63	3	5	10	143	136
-7	7	9	69	71	0	9	9	70	64	5	1	10	186	179	4	3	10	208	220	4	5	10	96	99
-6	7	9	88	83	1	9	9	65	72	6	1	10	121	104	5	3	10	67	71	5	5	10	154	155
-5	7	9	53	53	2	9	9	28	27	8	1	10	80	73	6	3	10	78	73	6	5	10	48	51
-4	7	9	105	106	3	9	9	56	54	-10	2	10	65	68	7	3	10	71	55	7	5	10	26	31
-3	7	9	49	56	4	9	9	32	25	-7	2	10	32	32	8	3	10	49	50	-9	6	10	52	43
-2	7	9	81	79	5	9	9	50	48	-6	2	10	70	56	-10	4	10	36	44	-7	6	10	54	52
-1	7	9	60	61	6	9	9	27	30	-5	2	10	120	130	-9	4	10	42	36	-6	6	10	47	44
0	7	9	151	159	-9	0	10	75	80	-4	2	10	128	135	-8	4	10	74	74	-5	6	10	102	98
1	7	9	153	136	-8	0	10	136	133	-3	2	10	192	196	-7	4	10	129	132	-4	6	10	117	103
2	7	9	141	137	-7	0	10	146	138	-2	2	10	119	130	-6	4	10	65	51	-3	6	10	99	97
3	7	9	55	59	-6	0	10	141	139	-1	2	10	74	77	-5	4	10	211	211	-2	6	10	153	150
4	7	9	83	74	-5	0	10	172	175	0	2	10	198	186	-4	4	10	91	80	-1	6	10	120	125
5	7	9	49	44	-4	0	10	90	78	1	2	10	140	130	-3	4	10	242	232	0	6	10	117	112
6	7	9	52	49	-3	0	10	135	142	2	2	10	36	35	-2	4	10	49	55	1	6	10	168	215
-8	8	9	64	57	-2	0	10	208	190	3	2	10	125	133	-1	4	10	173	170	2	6	10	33	40
-7	8	9	34	37	-1	0	10	328	327	4	2	10	171	162	0	4	10	95	99	3	6	10	89	98
-6	8	9	94	95	0	0	10	36	34	5	2	10	100	85	1	4	10	174	184	4	6	10	89	90
-5	8	9	100	90	1	0	10	164	164	6	2	10	46	51	2	4	10	58	48	5	6	10	34	29
-4	8	9	117	121	2	0	10	257	257	7	2	10	80	74	3	4	10	228	241	6	6	10	29	24
-3	8	9	62	67	3	0	10	127	126	8	2	10	50	51	4	4	10	96	101	-8	7	10	39	40
-2	8	9	64	58	7	0	10	62	46	-10	3	10	64	66	5	4	10	80	85	-7	7	10	53	46
-1	8	9	64	56	-9	1	10	39	41	-9	3	10	50	42	6	4	10	99	98	-6	7	10	68	76
0	8	9	68	72	-8	1	10	68	69	-8	3	10	89	81	7	4	10	35	44	-4	7	10	96	102
1	8	9	36	43	-6	1	10	164	156	-7	3	10	79	80	-9	5	10	34	39	-3	7	10	72	79
2	8	9	44	35	-5	1	10	105	102	-6	3	10	131	130	-7	5	10	37	39	-1	7	10	61	57
4	8	9	58	52	-4	1	10	126	134	-5	3	10	98	104	-5	5	10	44	46	0	7	10	65	67
7	8	9	22	17	-3	1	10	153	128	-4	3	10	102	107	-4	5	10	196	210	2	7	10	35	36
-8	9	9	43	41	-2	1	10	124	125	-3	3	10	192	218	-3	5	10	80	52	3	7	10	63	50
-7	9	9	70	71	-1	1	10	156	173	-2	3	10	154	175	-2	5	10	79	76	4	7	10	33	36
-5	9	9	91	86	0	1	10	115	113	-1	3	10	37	85	-1	5	10	152	143	5	7	10	25	28
-4	9	9	70	62	1	1	10	93	101	0	3	10	74	65	0	5	10	103	114	6	7	10	37	34
-3	9	9	84	75	2	1	10	88	85	1	3	10	86	84	1	5	10	112	100	7	7	10	51	61

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-8	8	10	31	25	4	0	11	45	33	7	2	11	63	59	6	4	11	24	26	-2	7	11	39	33
-7	8	10	21	11	5	0	11	36	25	-10	3	11	37	38	7	4	11	53	44	-1	7	11	135	120
-6	8	10	86	76	7	0	11	48	31	-9	3	11	24	23	-9	5	11	41	44	0	7	11	84	92
-5	8	10	30	28	8	0	11	36	34	-8	3	11	86	71	-6	5	11	31	28	1	7	11	68	61
-4	8	10	97	95	-10	1	11	41	40	-7	3	11	113	119	-5	5	11	53	55	2	7	11	87	81
-3	8	10	194	214	-8	1	11	87	72	-6	3	11	85	80	-4	5	11	115	117	3	7	11	55	53
-2	8	10	26	25	-7	1	11	63	52	-5	3	11	64	68	-3	5	11	73	68	4	7	11	26	25
-1	8	10	78	73	-6	1	11	157	154	-3	3	11	111	101	-2	5	11	98	102	5	7	11	55	55
0	8	10	56	54	-5	1	11	46	48	-2	3	11	127	126	-1	5	11	105	105	6	7	11	25	23
1	8	10	76	67	-4	1	11	112	119	-1	3	11	195	205	1	5	11	151	160	-7	8	11	64	60
2	8	10	80	81	-3	1	11	113	108	0	3	11	48	48	2	5	11	84	87	-5	8	11	90	78
4	8	10	60	59	-2	1	11	99	95	1	3	11	73	67	3	5	11	63	58	-3	8	11	52	41
6	8	10	44	39	-1	1	11	83	84	2	3	11	30	33	4	5	11	106	117	-2	8	11	176	165
-7	9	10	65	77	0	1	11	109	110	3	3	11	63	46	5	5	11	34	24	-1	8	11	73	67
-6	9	10	61	55	1	1	11	73	79	4	3	11	96	101	6	5	11	59	63	0	8	11	37	38
-4	9	10	26	32	2	1	11	109	115	5	3	11	58	56	-9	6	11	79	74	2	8	11	51	41
-2	9	10	97	108	3	1	11	50	55	6	3	11	34	35	-8	6	11	31	25	3	8	11	53	47
-1	9	10	41	52	4	1	11	82	81	7	3	11	29	28	-7	6	11	79	73	4	8	11	72	69
0	9	10	50	50	5	1	11	48	53	8	3	11	35	38	-6	6	11	70	60	5	8	11	38	33
1	9	10	106	121	6	1	11	77	82	-10	4	11	39	39	-5	6	11	77	79	6	8	11	33	41
3	9	10	57	52	-10	2	11	38	17	-9	4	11	39	42	-4	6	11	61	65	-7	9	11	32	34
5	9	10	38	35	-8	2	11	26	36	-7	4	11	42	44	-3	6	11	130	147	-6	9	11	28	29
-10	0	11	43	41	-7	2	11	99	93	-6	4	11	124	125	-2	6	11	55	51	-4	9	11	20	19
-9	0	11	79	66	-6	2	11	73	64	-5	4	11	101	98	-1	6	11	101	105	-3	9	11	79	95
-8	0	11	95	105	-5	2	11	44	45	-4	4	11	61	73	0	6	11	136	120	-2	9	11	42	38
-6	0	11	31	19	-4	2	11	146	149	-3	4	11	117	137	1	6	11	42	49	-1	9	11	66	65
-5	0	11	131	130	-3	2	11	184	181	-2	4	11	97	79	2	6	11	103	107	0	9	11	37	32
-3	0	11	91	90	-1	2	11	136	128	-1	4	11	63	70	3	6	11	54	47	1	9	11	82	90
-2	0	11	94	79	0	2	11	139	132	0	4	11	240	241	5	6	11	64	68	2	9	11	16	16
-1	0	11	56	59	1	2	11	26	19	1	4	11	42	55	-7	7	11	33	26	4	9	11	35	44
0	0	11	152	138	2	2	11	105	99	2	4	11	84	86	-6	7	11	78	72	5	9	11	31	30
1	0	11	30	18	3	2	11	131	129	3	4	11	65	75	-5	7	11	33	36	-8	0	12	141	130
2	0	11	29	17	4	2	11	110	125	4	4	11	67	66	-4	7	11	37	37	-7	0	12	52	57
3	0	11	143	140	6	2	11	40	47	5	4	11	94	98	-3	7	11	59	54	-6	0	12	110	104

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-5	0	12	33	42	1	2	12	149	159	3	4	12	114	109	-7	7	12	49	26	-3	0	13	37	26
-4	0	12	69	80	2	2	12	48	45	4	4	12	34	45	-5	7	12	103	105	-1	0	13	130	109
-2	0	12	69	67	3	2	12	153	151	5	4	12	62	55	-4	7	12	56	51	0	0	13	70	61
-1	0	12	173	169	5	2	12	85	94	6	4	12	56	62	-3	7	12	38	48	1	0	13	132	116
0	0	12	42	49	6	2	12	53	47	7	4	12	23	20	-1	7	12	58	52	2	0	13	85	92
1	0	12	128	130	7	2	12	30	30	-8	5	12	58	51	0	7	12	92	100	3	0	13	90	69
2	0	12	68	73	-9	3	12	66	68	-7	5	12	42	38	1	7	12	117	109	4	0	13	62	61
5	0	12	70	37	-8	3	12	70	76	-6	5	12	107	109	2	7	12	42	52	5	0	13	35	44
6	0	12	69	57	-7	3	12	104	95	-5	5	12	54	58	3	7	12	49	53	6	0	13	56	57
7	0	12	48	45	-6	3	12	64	62	-4	5	12	59	55	5	7	12	29	31	7	0	13	36	46
-8	1	12	83	79	-5	3	12	79	87	-3	5	12	157	151	-7	8	12	31	46	-7	1	13	49	40
-7	1	12	120	127	-4	3	12	91	104	-2	5	12	115	100	-6	8	12	41	37	-6	1	13	51	45
-6	1	12	149	151	-3	3	12	98	98	-1	5	12	98	96	-5	8	12	57	49	-5	1	13	100	101
-5	1	12	63	67	-2	3	12	138	137	0	5	12	211	217	-4	8	12	38	29	-4	1	13	55	53
-4	1	12	55	53	-1	3	12	230	226	1	5	12	96	98	-3	8	12	47	45	-3	1	13	65	71
-2	1	12	122	124	0	3	12	90	91	2	5	12	66	69	-2	8	12	26	27	-2	1	13	42	37
-1	1	12	165	165	1	3	12	135	128	3	5	12	26	18	0	8	12	94	91	0	1	13	137	145
0	1	12	137	139	2	3	12	86	95	4	5	12	59	61	1	8	12	27	29	2	1	13	51	46
1	1	12	75	91	3	3	12	77	78	5	5	12	41	41	2	8	12	87	76	3	1	13	81	68
2	1	12	96	85	4	3	12	89	85	6	5	12	32	34	3	8	12	31	33	5	1	13	64	62
3	1	12	70	71	5	3	12	85	95	-8	6	12	56	52	4	8	12	30	40	7	1	13	47	36
4	1	12	129	131	6	3	12	35	35	-7	6	12	64	64	5	8	12	31	66	-8	2	13	58	55
5	1	12	50	50	7	3	12	47	37	-6	6	12	55	50	-6	9	12	38	38	-7	2	13	34	54
7	1	12	64	60	-9	4	12	58	59	-5	6	12	92	88	-4	9	12	40	15	-6	2	13	100	96
-10	2	12	30	26	-7	4	12	37	37	-4	6	12	25	16	-3	9	12	78	64	-5	2	13	67	63
-9	2	12	59	63	-6	4	12	47	52	-3	6	12	66	64	-2	9	12	82	79	-4	2	13	86	72
-8	2	12	23	27	-5	4	12	52	44	-2	6	12	132	119	-1	9	12	110	96	-3	2	13	67	68
-7	2	12	81	83	-4	4	12	89	98	-1	6	12	91	95	0	9	12	44	39	-2	2	13	35	45
-6	2	12	90	78	-3	4	12	53	64	0	6	12	71	62	1	9	12	62	66	-1	2	13	126	122
-4	2	12	117	121	-2	4	12	101	105	1	6	12	114	111	3	9	12	23	17	0	2	13	91	89
-3	2	12	92	95	-1	4	12	67	57	2	6	12	53	44	4	9	12	41	40	1	2	13	167	165
-2	2	12	197	173	0	4	12	68	71	3	6	12	46	49	-8	0	13	30	25	2	2	13	62	58
-1	2	12	87	102	1	4	12	114	117	4	6	12	35	37	-6	0	13	123	120	3	2	13	97	86
0	2	12	177	178	2	4	12	105	103	5	6	12	35	29	-5	0	13	52	50	4	2	13	93	101

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-9	3	13	57	54	-3	5	13	72	63	-4	8	13	42	44	-2	1	14	95	102	3	3	14	48	41
-8	3	13	45	48	-1	5	13	48	51	-3	8	13	29	22	0	1	14	141	127	4	3	14	66	64
-7	3	13	52	52	0	5	13	50	62	-2	8	13	24	23	1	1	14	79	82	5	3	14	36	28
-5	3	13	89	82	1	5	13	69	64	-1	8	13	85	75	2	1	14	98	104	-8	4	14	57	71
-4	3	13	50	55	2	5	13	95	85	0	8	13	49	42	3	1	14	93	95	-7	4	14	37	35
-3	3	13	52	45	3	5	13	63	57	1	8	13	84	88	4	1	14	111	110	-6	4	14	55	53
-2	3	13	80	77	4	5	13	69	64	2	8	13	25	23	5	1	14	87	74	-5	4	14	50	46
-1	3	13	35	33	-8	6	13	38	40	3	8	13	32	35	-9	2	14	27	34	-4	4	14	64	71
0	3	13	161	155	-6	6	13	70	67	4	8	13	30	30	-8	2	14	34	29	-3	4	14	68	74
1	3	13	69	72	-5	6	13	34	41	-5	9	13	42	30	-7	2	14	60	52	-2	4	14	50	56
2	3	13	46	42	-4	6	13	113	99	-4	9	13	32	30	-6	2	14	62	62	-1	4	14	62	65
3	3	13	26	40	-3	6	13	38	37	-3	9	13	43	43	-5	2	14	34	26	0	4	14	60	60
5	3	13	70	61	-2	6	13	47	45	-2	9	13	40	42	-4	2	14	28	22	1	4	14	55	48
6	3	13	35	30	-1	6	13	104	98	0	9	13	67	66	-3	2	14	35	33	2	4	14	100	102
-8	4	13	59	61	0	6	13	58	58	1	9	13	49	48	-2	2	14	109	104	3	4	14	71	77
-7	4	13	38	40	1	6	13	98	94	2	9	13	41	45	-1	2	14	83	75	4	4	14	41	42
-6	4	13	33	32	2	6	13	64	62	3	9	13	15	14	0	2	14	81	85	5	4	14	39	39
-5	4	13	69	73	3	6	13	53	50	-7	0	14	42	50	1	2	14	51	48	-7	5	14	77	75
-4	4	13	40	36	4	6	13	29	28	-6	0	14	86	90	2	2	14	122	124	-6	5	14	77	70
-3	4	13	48	42	5	6	13	36	33	-5	0	14	89	72	3	2	14	80	80	-5	5	14	47	48
-2	4	13	116	129	-7	7	13	55	55	-4	0	14	166	170	4	2	14	69	62	-4	5	14	32	39
-1	4	13	69	70	-6	7	13	24	33	-3	0	14	74	71	5	2	14	27	18	-3	5	14	33	29
0	4	13	70	71	-5	7	13	65	69	-2	0	14	45	38	6	2	14	44	47	-2	5	14	58	59
1	4	13	67	59	-4	7	13	55	51	-1	0	14	39	39	-8	3	14	42	42	-1	5	14	100	99
2	4	13	77	81	-3	7	13	59	53	1	0	14	196	202	-7	3	14	87	96	0	5	14	73	61
3	4	13	98	91	-2	7	13	57	56	2	0	14	60	48	-6	3	14	68	62	1	5	14	109	111
4	4	13	50	56	-1	7	13	42	39	4	0	14	99	87	-5	3	14	52	55	2	5	14	63	57
5	4	13	46	43	0	7	13	104	107	5	0	14	66	70	-4	3	14	93	88	3	5	14	87	85
6	4	13	22	23	1	7	13	63	48	6	0	14	45	39	-3	3	14	83	77	4	5	14	34	28
-8	5	13	62	56	2	7	13	86	83	-7	1	14	85	74	-2	3	14	115	111	5	5	14	49	58
-7	5	13	69	60	4	7	13	61	69	-6	1	14	102	95	-1	3	14	31	33	-6	6	14	61	55
-6	5	13	61	58	5	7	13	47	49	-5	1	14	117	115	0	3	14	93	97	-5	6	14	49	45
-5	5	13	69	66	-6	8	13	50	38	-4	1	14	53	66	1	3	14	101	85	-3	6	14	54	51
-4	5	13	86	72	-5	8	13	28	25	-3	1	14	71	67	2	3	14	82	90	-2	6	14	25	28

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-7	6	14	72	69	2	0	15	112	95	4	3	15	51	52	2	7	15	20	18	-1	3	16	77	67
2	6	14	81	76	5	0	15	53	53	5	3	15	32	34	-3	8	15	73	82	0	3	16	59	57
3	6	14	29	26	-8	1	15	49	49	-7	4	15	54	64	-2	8	15	38	36	1	3	16	100	100
4	6	14	58	59	-4	1	15	110	95	-6	4	15	33	34	-1	8	15	39	31	4	3	16	41	54
-6	7	14	43	51	-3	1	15	70	67	-5	4	15	64	67	0	8	15	23	25	-6	4	16	22	26
-5	7	14	62	64	-2	1	15	47	44	-4	4	15	24	21	1	8	15	24	23	-5	4	16	29	32
-4	7	14	58	62	-1	1	15	77	34	-3	4	15	87	86	-7	0	16	30	30	-4	4	16	49	44
-3	7	14	47	38	0	1	15	55	50	-2	4	15	48	51	-5	0	16	100	99	-3	4	16	54	45
-2	7	14	35	38	1	1	15	99	88	-1	4	15	53	50	-4	0	16	58	52	-2	4	16	105	117
-1	7	14	26	19	4	1	15	73	73	0	4	15	78	79	-2	0	16	95	92	-1	4	16	38	40
0	7	14	58	61	5	1	15	44	47	2	4	15	56	51	-1	0	16	48	47	0	4	16	79	83
1	7	14	60	59	-8	2	15	47	49	3	4	15	37	46	0	0	16	110	108	1	4	16	47	46
2	7	14	71	70	-6	2	15	24	25	4	4	15	58	63	2	0	16	53	50	3	4	16	46	59
3	7	14	46	43	-5	2	15	62	59	-6	5	15	41	42	-7	1	16	37	37	-5	5	16	54	51
-5	8	14	57	57	-4	2	15	35	41	-4	5	15	58	55	-4	1	16	73	78	-4	5	16	55	55
-4	8	14	48	43	-3	2	15	38	45	-3	5	15	41	33	-3	1	16	37	31	-3	5	16	25	19
-3	8	14	42	42	-2	2	15	71	67	-2	5	15	80	77	-2	1	16	97	89	-2	5	16	41	35
-1	8	14	55	56	0	2	15	49	42	-1	5	15	43	34	-1	1	16	81	72	-1	5	16	79	79
0	8	14	68	59	1	2	15	46	48	2	5	15	42	43	0	1	16	84	82	0	5	16	50	46
1	8	14	38	30	2	2	15	39	42	3	5	15	41	37	1	1	16	41	35	1	5	16	38	37
2	8	14	52	48	3	2	15	40	48	-6	6	15	42	36	3	1	16	36	26	2	5	16	24	29
3	8	14	45	41	4	2	15	46	37	-5	6	15	36	31	4	1	16	39	38	-5	6	16	49	52
-4	9	14	40	38	5	2	15	32	35	-4	6	15	43	42	-5	2	16	31	25	-4	6	16	32	30
-2	9	14	24	27	-8	3	15	28	33	-3	6	15	71	72	-3	2	16	117	124	-3	6	16	30	29
-1	9	14	17	14	-7	3	15	56	52	-1	6	15	28	22	-1	2	16	77	81	-2	6	16	44	41
0	9	14	14	21	-6	3	15	71	59	0	6	15	29	23	0	2	16	52	46	-1	6	16	46	39
1	9	14	37	35	-5	3	15	38	35	2	6	15	21	22	1	2	16	42	40	0	6	16	21	22
-7	0	15	60	50	-4	3	15	52	51	3	6	15	37	34	2	2	16	34	42	1	6	16	51	47
-6	0	15	30	35	-3	3	15	81	75	-5	7	15	31	30	3	2	16	23	31	-4	7	16	29	34
-5	0	15	143	169	-2	3	15	34	39	-4	7	15	72	73	4	2	16	41	44	-3	7	16	52	63
-4	0	15	39	32	-1	3	15	76	70	-2	7	15	66	67	-6	3	16	59	68	-2	7	16	57	56
-2	0	15	88	75	1	3	15	54	47	-1	7	15	24	25	-5	3	16	43	49	-1	7	16	29	28
-1	0	15	113	103	2	3	15	49	37	0	7	15	54	49	-3	3	16	44	48	0	7	16	45	49
0	0	15	70	64	3	3	15	100	97	1	7	15	63	58	-2	3	16	38	45	-6	0	17	37	36

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR GIRVEN P2(1)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-5	0	17	28	34	-5	2	17	41	40	0	3	17	43	44	0	5	17	35	28	-4	2	18	40	48
-4	0	17	68	65	-4	2	17	77	66	1	3	17	40	37	-2	6	17	51	55	-2	2	18	55	60
-3	0	17	50	57	-2	2	17	75	79	-5	4	17	30	24	-1	6	17	35	36	-1	2	18	66	72
-2	0	17	83	67	-1	2	17	23	26	-3	4	17	27	30	0	6	17	51	60	0	2	18	32	32
-1	0	17	47	47	0	2	17	91	84	-2	4	17	70	66	-2	0	18	45	45	1	2	18	41	44
1	0	17	60	48	1	2	17	31	25	-1	4	17	35	37	-1	0	18	38	38	-4	3	18	29	32
2	0	17	56	56	3	2	17	45	49	0	4	17	21	20	1	0	18	56	76	-3	3	18	24	23
-5	1	17	54	51	-6	3	17	40	51	1	4	17	45	52	-4	1	18	45	40	-2	3	18	73	68
-4	1	17	53	54	-5	3	17	24	27	2	4	17	25	30	-3	1	18	73	76	-1	3	18	34	32
-3	1	17	89	90	-4	3	17	32	32	-4	5	17	32	46	-2	1	18	38	41	0	3	18	35	38
-1	1	17	86	78	-3	3	17	40	23	-3	5	17	29	33	-1	1	18	45	45	-3	4	18	27	32
1	1	17	41	38	-2	3	17	28	24	-2	5	17	36	37	0	1	18	67	72	-2	4	18	21	26
-6	2	17	25	32	-1	3	17	83	84	-1	5	17	40	37	-5	2	18	27	35	-1	4	18	28	29

APPENDIX D

TABLE XVIII

List of Structure Factors for Anidoxime, BRL 11870

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870 - anidoxime

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
3	0	0	392	430	4	6	0	31	11	0	14	0	163	169	0	4	1	693	-749	0	5	1	131	-106
5	0	0	234	-234	5	6	0	252	233	2	14	0	147	-145	2	4	1	358	375	1	5	1	185	-186
6	0	0	223	-130	6	6	0	192	196	4	14	0	96	98	3	4	1	112	-115	2	5	1	48	-50
1	1	0	399	385	1	7	0	358	-351	6	14	0	98	-108	4	4	1	150	-129	5	5	1	73	-79
3	1	0	171	161	2	7	0	294	285	1	15	0	261	242	6	4	1	134	-124	6	5	1	200	-191
4	1	0	92	-75	4	7	0	91	-93	2	15	0	166	154	-5	5	1	79	69	-6	6	1	44	41
5	1	0	34	28	6	7	0	80	88	5	15	0	117	123	-4	5	1	123	-104	-5	6	1	229	-231
6	1	0	152	-141	0	8	0	358	-403	6	15	0	51	45	-3	5	1	209	-201	-3	6	1	44	-27
0	2	0	364	-344	1	8	0	688	684	0	16	0	166	147	-2	5	1	268	249	-2	6	1	264	257
1	2	0	316	-320	2	8	0	126	123	1	16	0	132	-126	-1	5	1	1051	-1028	-1	6	1	481	479
3	2	0	42	-36	3	8	0	150	-146	2	16	0	173	-163	0	5	1	342	393	0	6	1	403	-409
4	2	0	332	350	4	8	0	345	-335	4	16	0	122	121	1	5	1	296	-293	1	6	1	851	863
5	2	0	103	-111	5	8	0	169	167	5	16	0	84	-91	3	5	1	215	206	2	6	1	132	142
6	2	0	168	-157	2	9	0	206	-215	1	17	0	140	-152	4	5	1	278	279	3	6	1	212	-231
1	3	0	214	185	3	9	0	120	-120	2	17	0	81	-80	5	5	1	64	73	4	6	1	365	354
2	3	0	76	63	4	9	0	49	-45	0	18	0	202	170	6	5	1	105	100	5	6	1	154	157
3	3	0	563	555	5	9	0	208	-203	2	18	0	135	-116	-6	6	1	399	381	6	6	1	133	-131
4	3	0	175	-180	0	10	0	219	-228	5	18	0	56	-66	-5	6	1	167	-142	-6	7	1	70	82
5	3	0	102	-112	1	10	0	133	138	4	19	0	42	-40	-4	6	1	168	-162	-5	7	1	56	41
6	3	0	183	-173	2	10	0	91	94	0	20	0	156	-167	-3	6	1	443	437	-4	7	1	44	54
1	4	0	760	-759	4	10	0	55	-60	3	20	0	71	-59	-2	6	1	721	749	-2	7	1	209	-199
2	4	0	62	47	6	10	0	47	48	1	21	0	63	-52	-1	6	1	1698	-1642	-1	7	1	561	532
3	4	0	194	168	3	11	0	247	-243	-6	1	1	38	-28	0	6	1	69	-20	0	7	1	86	95
4	4	0	425	-371	4	11	0	233	244	-5	1	1	297	298	1	6	1	441	403	1	7	1	209	-182
1	5	0	267	-246	5	11	0	94	-94	-4	1	1	111	-109	2	6	1	307	-277	2	7	1	378	-391
2	5	0	170	164	6	11	0	156	-146	0	1	1	240	-218	3	6	1	670	-642	3	7	1	147	151
3	5	0	164	177	2	12	0	173	168	2	1	1	750	792	4	6	1	77	-51	4	7	1	55	65
4	5	0	106	-117	3	12	0	132	-130	3	1	1	517	-519	5	6	1	244	245	5	7	1	320	-322
5	5	0	205	185	6	12	0	52	42	4	1	1	303	-316	6	6	1	106	83	-6	8	1	47	-42
6	5	0	340	313	1	13	0	143	144	5	1	1	348	308	-6	7	1	137	-124	-5	8	1	119	136
0	6	0	791	-786	2	13	0	83	-58	-6	2	1	292	282	-5	7	1	289	-275	-4	8	1	203	-193
1	6	0	268	-251	3	13	0	210	-183	-4	2	1	205	-193	-4	7	1	105	-84	-3	8	1	188	195
2	6	0	242	277	4	13	0	239	242	-2	2	1	285	303	-3	7	1	381	349	-2	8	1	285	-286
3	6	0	259	-254	6	13	0	91	-88	-1	2	1	499	486	-2	7	1	318	-315	-1	8	1	76	-56

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870 ..

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
0	8	1	174	197	-4	12	1	283	291	-5	17	1	153	171	6	1	2	108	104	1	4	2	401	-416
2	8	1	63	-59	-2	12	1	304	-335	-3	17	1	198	-213	5	1	2	123	-135	2	4	2	658	711
3	8	1	189	189	-1	12	1	342	337	-2	17	1	92	92	6	1	2	77	79	4	4	2	220	199
4	8	1	45	-67	0	12	1	175	175	-1	17	1	148	144	-6	2	2	74	64	6	4	2	151	-142
5	8	1	63	-66	1	12	1	290	-301	0	17	1	151	-137	-5	2	2	58	-70	-5	5	2	105	107
-6	9	1	83	76	2	12	1	172	-180	2	17	1	137	94	-4	2	2	213	-191	-4	5	2	251	253
-5	9	1	47	46	3	12	1	250	234	3	17	1	161	-141	-3	2	2	448	437	-3	5	2	204	165
-4	9	1	205	210	5	12	1	72	-69	4	17	1	192	-194	-1	2	2	1377	-1388	-2	5	2	145	113
-3	9	1	136	139	6	12	1	160	158	5	17	1	40	56	0	2	2	335	318	-1	5	2	1738	1672
-1	9	1	166	174	-6	13	1	64	-76	-1	18	1	94	-92	1	2	2	110	106	0	5	2	134	123
0	9	1	486	466	-5	13	1	190	-210	0	18	1	165	-164	2	2	2	178	-190	1	5	2	413	-377
1	9	1	133	106	-4	13	1	133	-128	5	18	1	56	64	3	2	2	284	293	2	5	2	63	37
2	9	1	92	-101	-2	13	1	177	191	-2	19	1	105	82	4	2	2	68	74	3	5	2	750	766
4	9	1	36	49	-1	13	1	128	-160	0	19	1	118	-104	5	2	2	42	45	4	5	2	333	-335
5	9	1	273	-267	0	13	1	91	-87	2	19	1	76	51	6	2	2	106	97	5	5	2	157	-159
6	9	1	49	36	1	13	1	130	145	4	19	1	133	-117	-6	3	2	92	73	6	5	2	112	82
-6	10	1	105	-104	-6	14	1	73	-72	-4	20	1	45	-38	-5	3	2	221	209	-6	6	2	268	-233
-5	10	1	70	-69	-3	14	1	63	-72	1	20	1	60	66	-4	3	2	392	379	-5	6	2	244	228
-4	10	1	80	66	-1	14	1	339	366	0	21	1	68	42	-3	3	2	75	-82	-4	6	2	71	-96
-3	10	1	211	-223	0	14	1	92	78	2	21	1	62	-72	-2	3	2	314	-336	-3	6	2	87	60
-2	10	1	244	-259	2	14	1	103	90	0	22	1	74	77	-1	3	2	661	668	-2	6	2	225	238
-1	10	1	161	181	4	14	1	50	57	1	0	2	846	822	0	3	2	1141	-1331	-1	6	2	620	640
1	10	1	473	-466	-6	15	1	68	74	2	0	2	956	-949	1	3	2	150	-148	0	6	2	67	-92
2	10	1	287	297	-5	15	1	65	73	3	0	2	432	-498	3	3	2	461	443	1	6	2	385	-383
5	10	1	254	-256	-2	15	1	67	68	4	0	2	129	156	4	3	2	41	-42	2	6	2	283	-251
-4	11	1	71	84	-1	15	1	96	37	5	0	2	77	-74	5	3	2	53	42	3	6	2	67	-61
-2	11	1	345	-361	0	15	1	91	-69	6	0	2	395	-361	6	3	2	204	200	4	6	2	57	-45
-1	11	1	238	-238	1	15	1	88	-76	-6	1	2	162	-150	-6	4	2	165	-170	6	6	2	196	173
2	11	1	216	-232	2	15	1	120	151	-4	1	2	92	93	-5	4	2	57	-47	-3	7	2	80	-84
3	11	1	68	66	-6	16	1	104	103	-2	1	2	232	-206	-4	4	2	78	85	-4	7	2	175	148
4	11	1	205	210	-4	16	1	125	-138	0	1	2	337	336	-3	4	2	136	-135	-3	7	2	358	-356
5	11	1	232	254	-2	16	1	98	110	1	1	2	561	506	-2	4	2	78	-62	-2	7	2	106	-135
-6	12	1	142	-151	-1	16	1	250	-251	2	1	2	567	-588	-1	4	2	1186	1212	0	7	2	116	105
-5	12	1	207	219	3	16	1	74	-79	3	1	2	314	-303	0	4	2	165	165	1	7	2	323	-315

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	7	4	236	-224	6	10	2	50	50	2	14	2	194	-176	-2	1	3	474	510	-6	4	3	247	238
4	7	4	50	32	-6	11	2	85	88	6	14	2	58	-51	-1	1	3	320	-304	-4	4	3	121	-113
5	7	4	384	-391	-4	11	2	57	-66	-1	15	2	126	134	0	1	3	474	-508	-3	4	3	162	-155
6	7	4	75	79	-2	11	2	75	82	1	15	2	156	176	1	1	3	335	-347	-2	4	3	45	-18
-6	8	4	95	96	-1	11	2	381	-361	3	15	2	111	-101	2	1	3	693	714	-1	4	3	388	453
-5	8	4	246	248	0	11	2	170	-168	4	15	2	129	-130	3	1	3	393	-382	0	4	3	704	-751
-4	8	4	92	-82	1	11	2	291	304	-5	16	2	138	-145	4	1	3	530	-498	1	4	3	1174	1189
-3	8	4	282	-271	2	11	2	67	59	-2	16	2	72	-67	5	1	3	73	66	2	4	3	166	161
-2	8	4	116	115	3	11	2	112	-119	-1	16	2	326	-319	6	1	3	201	183	3	4	3	190	-203
-1	8	4	240	256	4	11	2	346	340	0	16	2	117	108	-6	2	3	77	-72	4	4	3	196	201
0	8	4	237	-256	5	11	2	232	256	1	16	2	217	211	-5	2	3	149	-147	5	4	3	205	217
1	8	4	97	-109	6	11	2	83	-84	2	16	2	136	-105	-4	2	3	94	-103	6	4	3	108	-119
2	8	4	527	527	-4	12	2	88	-81	5	16	2	64	-55	-3	2	3	145	-130	-5	5	3	39	40
3	8	4	172	-168	-2	12	2	80	-98	0	17	2	123	-103	-2	2	3	196	212	-4	5	3	110	105
4	8	4	282	-281	1	12	2	63	65	1	17	2	94	-78	-1	2	3	605	567	-3	5	3	306	287
5	8	4	72	-76	2	12	2	98	-104	4	17	2	92	-91	0	2	3	722	837	-2	5	3	176	175
6	8	4	101	96	3	12	2	96	93	-3	18	2	67	59	1	2	3	486	487	0	5	3	348	362
-6	9	4	75	-72	4	12	2	69	66	-2	18	2	122	-100	2	2	3	235	-218	1	5	3	361	339
-5	9	4	313	-299	5	12	2	80	90	0	18	2	107	101	3	2	3	621	606	2	5	3	262	-259
-4	9	4	199	-196	-6	13	2	168	170	2	18	2	108	-102	5	2	3	47	56	4	5	3	484	463
-3	9	4	97	109	-5	13	2	83	86	4	18	2	42	49	6	2	3	83	-82	5	5	3	56	-50
-2	9	4	462	-415	-4	13	2	136	-129	5	18	2	72	-69	-6	3	3	226	205	6	5	3	96	80
-1	9	4	231	-210	-3	13	2	145	152	-3	19	2	110	-115	-5	3	3	57	45	-6	6	3	102	106
1	9	4	290	294	-2	13	2	386	406	-2	19	2	53	-42	-4	3	3	454	-412	-5	6	3	102	114
3	9	4	333	-332	-1	13	2	222	-226	1	19	2	76	-72	-3	3	3	180	-175	-4	6	3	210	-226
4	9	4	45	-54	2	13	2	90	95	3	19	2	111	113	-2	3	3	122	-137	-3	6	3	254	242
5	9	4	73	65	3	13	2	181	-188	-2	20	2	199	-8	-1	3	3	1239	1271	-2	6	3	429	42.
-5	10	4	149	145	5	13	2	61	71	0	20	2	87	75	0	3	3	368	-386	-1	6	3	259	-274
-3	10	4	115	-122	-6	14	2	70	69	-2	21	2	93	-86	1	3	3	322	-311	0	6	3	423	-433
-2	10	4	188	-173	-5	14	2	88	-93	-1	21	2	86	92	2	3	3	86	-56	1	6	3	610	627
-1	10	4	150	-131	-4	14	2	95	111	1	21	2	78	-71	3	3	3	362	344	2	6	3	73	-69
0	10	4	189	-208	-2	14	2	247	258	-6	1	3	98	-111	4	3	3	98	-101	4	6	3	188	-185
1	10	4	135	133	-1	14	2	90	86	-4	1	3	270	240	5	3	3	71	-59	6	6	3	68	63
2	10	4	224	231	1	14	2	185	-177	-3	1	3	474	-472	6	3	3	157	-132	-6	7	3	154	-140

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-5	7	5	139	-152	2	10	5	229	-230	3	14	5	92	89	-6	1	6	148	-159	-6	4	6	60	52
-3	7	5	488	468	3	10	5	135	121	4	14	5	169	-160	-5	1	6	142	125	-5	4	6	103	98
-2	7	5	603	-748	4	10	5	78	66	5	14	5	134	-147	-4	1	6	63	60	-4	4	6	46	63
-1	7	5	417	-372	5	10	5	202	-207	6	14	5	67	56	-3	1	6	196	181	-3	4	6	84	86
0	7	5	187	215	6	10	5	62	56	0	15	5	164	-176	-2	1	6	260	-262	-2	4	6	380	379
4	7	5	346	341	-6	11	5	56	51	1	15	5	78	-64	-1	1	6	1385	1362	0	4	6	265	248
-6	8	5	135	123	-5	11	5	105	-115	4	15	5	117	-120	0	1	6	522	570	1	4	6	206	202
-5	8	5	111	-107	-3	11	5	68	-60	5	15	5	69	65	1	1	6	125	-127	2	4	6	116	-123
-4	8	5	175	161	-2	11	5	326	347	0	16	5	161	-150	2	1	6	81	-76	4	4	6	97	-101
-3	8	5	120	-110	0	11	5	165	160	2	17	5	255	216	3	1	6	119	104	5	4	6	94	-83
-2	8	5	102	-110	1	11	5	111	109	3	17	5	146	152	6	1	6	96	-84	6	4	6	194	201
0	8	5	372	-372	3	11	5	74	-60	4	17	5	98	-78	-5	2	6	330	-299	-6	5	6	48	-54
1	8	5	594	-589	4	11	5	110	108	-2	18	5	75	-69	-4	2	6	171	152	-5	5	6	343	-328
2	8	5	174	-148	5	11	5	64	-59	2	18	5	113	-107	-3	2	6	90	98	-4	5	6	379	370
3	8	5	218	-193	-6	12	5	255	251	5	18	5	39	43	-2	2	6	313	-311	-3	5	6	340	-338
5	8	5	109	117	-2	12	5	446	-495	-4	19	5	67	61	-1	2	6	576	613	-2	5	6	462	-491
-6	9	5	95	-92	-1	12	5	140	159	-1	19	5	107	105	0	2	6	269	235	0	5	6	412	394
-5	9	5	76	-92	0	12	5	278	269	0	19	5	92	-63	1	2	6	222	217	1	5	6	282	-231
-4	9	5	49	-23	1	12	5	274	-268	2	19	5	64	53	2	2	6	61	24	2	5	6	263	-272
-3	9	5	300	304	2	12	5	159	170	3	19	5	56	56	4	2	6	161	166	3	5	6	218	246
-2	9	5	657	-759	3	12	5	193	186	-1	20	5	93	-78	5	2	6	58	60	4	5	6	80	-67
-1	9	5	301	-258	4	12	5	76	77	0	20	5	103	-85	6	2	6	138	-151	5	5	6	391	-388
0	9	5	145	131	6	12	5	67	68	1	20	5	77	71	-6	3	6	289	-287	-6	6	6	34	39
1	9	5	249	236	-6	13	5	76	76	3	20	5	52	-46	-5	3	6	37	27	-3	6	6	247	217
2	9	5	405	-425	-5	13	5	86	80	-6	0	6	148	144	-4	3	6	406	391	-2	6	6	366	-379
3	9	5	61	-82	-3	13	5	77	81	-4	0	6	387	-372	-3	3	6	135	-132	-1	6	6	558	536
5	9	5	92	-101	-2	13	5	316	359	-3	0	6	168	178	-2	3	6	302	-296	1	6	6	442	-426
6	9	5	91	-92	1	13	5	96	-93	-2	0	6	560	-575	-1	3	6	89	108	4	6	6	179	-164
-6	10	5	183	-135	3	13	5	53	-55	-1	0	6	1606	-1528	1	3	6	454	-434	5	6	6	79	73
-5	10	5	83	-56	4	13	5	131	-135	0	0	6	815	-968	2	3	6	213	-225	6	6	6	73	64
-4	10	5	44	46	-2	14	5	195	178	1	0	6	463	492	3	3	6	310	305	-4	7	6	37	37
-2	10	5	86	92	-1	14	5	215	198	2	0	6	978	-1033	4	3	6	145	154	-3	7	6	193	167
-1	10	5	280	-249	0	14	5	108	81	4	0	6	369	360	5	3	6	96	-83	-2	7	6	412	-429
0	10	5	259	258	2	14	5	128	110	6	0	6	190	-207	6	3	6	322	316	-1	7	6	199	-182

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
0	7	4	110	111	-5	11	4	99	109	0	16	4	271	268	-2	2	5	102	-109	3	5	5	385	-377
1	7	4	318	332	-4	11	4	98	-94	1	16	4	224	204	-1	2	5	751	-768	4	5	5	170	169
2	7	4	436	-442	-2	11	4	440	490	2	16	4	75	-77	0	2	5	908	-929	5	5	5	262	262
3	7	4	211	225	-1	11	4	80	-89	4	16	4	93	91	1	2	5	461	-496	-5	6	5	67	75
4	7	4	103	112	0	11	4	223	-222	-6	17	4	32	-27	2	2	5	52	41	-4	6	5	57	-70
5	7	4	66	73	1	11	4	68	-82	-5	17	4	79	-71	3	2	5	61	68	-3	6	5	127	-117
6	7	4	85	-83	2	11	4	156	145	-2	17	4	129	-128	4	2	5	190	194	-2	6	5	188	-168
-6	8	4	87	-89	3	11	4	131	-126	2	17	4	76	70	-6	3	5	61	59	-1	6	5	268	259
-5	8	4	251	252	4	11	4	149	-164	3	17	4	89	91	-3	3	5	201	-212	0	6	5	123	122
-4	8	4	46	42	5	11	4	92	103	4	17	4	47	39	-2	3	5	234	229	2	6	5	268	268
-3	8	4	409	-416	6	11	4	60	-62	5	17	4	52	-41	-1	3	5	479	515	3	6	5	318	-326
-1	8	4	97	113	-2	12	4	83	-62	-3	18	4	144	125	0	3	5	284	277	4	6	5	144	-153
0	8	4	531	-526	1	12	4	105	-81	-2	18	4	73	71	1	3	5	106	119	5	6	5	121	121
1	8	4	76	-81	4	12	4	78	-78	-1	18	4	184	-195	2	3	5	302	-276	6	6	5	103	-91
2	8	4	422	414	5	12	4	66	73	1	18	4	82	63	4	3	5	108	101	-5	7	5	140	-137
4	8	4	94	89	-4	13	4	96	-84	2	18	4	122	-109	5	3	5	124	-112	-3	7	5	398	389
5	8	4	75	-66	-2	13	4	101	103	4	18	4	51	46	6	3	5	105	122	-2	7	5	384	336
6	8	4	82	67	-1	13	4	92	-85	-1	19	4	117	130	-6	4	5	131	118	-1	7	5	560	-513
-6	9	4	64	65	0	13	4	241	-237	1	20	4	63	-57	-5	4	5	341	309	0	7	5	116	110
-4	9	4	99	-93	1	13	4	350	350	0	21	4	104	102	-4	4	5	631	-611	1	7	5	244	225
-2	9	4	429	442	3	13	4	141	-140	-6	1	5	122	-141	-3	4	5	102	102	3	7	5	102	-102
-1	9	4	107	88	5	13	4	135	160	-4	1	5	267	263	-2	4	5	209	209	4	7	5	129	135
2	9	4	166	159	-2	14	4	124	112	-3	1	5	488	-479	-1	4	5	212	-184	5	7	5	164	-177
3	9	4	141	-133	-1	14	4	68	55	-2	1	5	485	-482	0	4	5	671	-685	6	7	5	70	-76
-6	10	4	106	-110	2	14	4	235	-219	-1	1	5	450	466	1	4	5	616	581	-6	8	5	82	-72
-5	10	4	71	64	4	14	4	116	109	0	1	5	965	-1045	2	4	5	96	-95	-5	8	5	94	-96
-4	10	4	48	-56	-6	15	4	41	35	2	1	5	209	187	5	4	5	181	180	-3	8	5	235	-242
-2	10	4	231	244	-4	15	4	51	-56	3	1	5	557	564	-6	5	5	151	139	-2	8	5	543	536
-1	10	4	81	-73	1	15	4	102	-106	4	1	5	460	-440	-5	5	5	72	82	-1	8	5	60	26
0	10	4	174	-161	6	15	4	75	68	6	1	5	90	77	-4	5	5	52	-38	0	8	5	207	-212
2	10	4	353	368	-5	16	4	109	-105	-6	2	5	98	97	-3	5	5	198	225	1	8	5	119	132
4	10	4	274	-270	-3	16	4	153	126	-5	2	5	182	-164	-2	5	5	113	-132	2	8	5	112	90
6	10	4	96	98	-2	16	4	144	-156	-4	2	5	168	154	0	5	5	92	71	3	8	5	155	170
-6	11	4	104	113	-1	16	4	96	-100	-3	2	5	654	624	2	5	5	127	-120	5	8	5	71	-88

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
6	8	5	57	57	-1	12	5	167	-160	2	17	5	119	95	-4	2	6	112	104	1	5	6	131	-124
-6	9	5	127	122	0	12	5	289	293	4	17	5	79	-67	-3	2	6	63	-47	2	5	6	93	-92
-5	9	5	126	-126	1	12	5	143	-176	-2	18	5	94	87	-2	2	6	363	373	3	5	6	161	153
-4	9	5	82	-67	2	12	5	304	-288	1	18	5	104	95	-1	2	6	211	237	4	5	6	59	-56
-3	9	5	205	205	3	12	5	134	148	3	18	5	116	-119	0	2	6	269	-250	5	5	6	436	-405
-1	9	5	331	-329	4	12	5	146	158	-6	19	5	55	40	1	2	6	535	534	-6	6	6	46	-45
0	9	5	362	374	5	12	5	119	-131	0	19	5	109	114	2	2	6	688	-723	-4	6	6	53	-49
1	9	5	276	-268	-5	13	5	118	122	-3	20	5	76	75	6	2	6	126	-133	-3	6	6	348	-363
2	9	5	106	-80	-3	13	5	225	-226	-2	20	5	83	66	-6	3	6	234	-237	-2	6	6	270	293
3	9	5	82	75	-2	13	5	234	-219	-1	20	5	71	-63	-5	3	6	206	-207	-1	6	6	245	219
4	9	5	204	197	0	13	5	132	-115	0	20	5	109	-93	-4	3	6	243	244	0	6	6	478	443
5	9	5	126	-127	5	13	5	100	140	-1	21	5	87	-84	-3	3	6	314	297	1	6	6	130	128
6	9	5	107	-92	-6	14	5	48	-60	-6	0	6	417	409	-2	3	6	639	-695	2	6	6	429	432
-6	10	5	75	87	-4	14	5	107	116	-5	0	6	384	-361	-1	3	6	385	358	3	6	6	116	107
-5	10	5	90	-85	-3	14	5	101	-99	-4	0	6	146	131	0	3	6	583	569	4	6	6	160	159
-4	10	5	157	165	-2	14	5	286	-266	-3	0	6	710	674	1	3	6	412	-389	5	6	6	194	-213
-3	10	5	303	287	0	14	5	104	91	-2	0	6	452	477	2	3	6	306	-293	6	6	6	63	47
0	10	5	261	246	1	14	5	327	-325	-1	0	6	1193	-1196	4	3	6	88	-84	-6	7	6	94	100
2	10	5	124	-115	3	14	5	152	142	0	0	6	480	-499	5	3	6	98	-99	-5	7	6	60	71
3	10	5	126	135	4	14	5	69	-65	1	0	6	218	234	-6	4	6	49	43	-3	7	6	111	113
4	10	5	151	-163	5	14	5	106	-93	2	0	6	270	233	-5	4	6	130	-118	-2	7	6	154	145
5	10	5	111	111	-3	15	5	113	-115	4	0	6	188	206	-3	4	6	199	-191	-1	7	6	216	-206
-6	11	5	89	-83	-2	15	5	183	163	6	0	6	65	62	-2	4	6	614	-639	0	7	6	179	165
-4	11	5	149	-166	-1	15	5	103	86	-6	1	6	72	-72	-1	4	6	169	-163	1	7	6	90	67
-3	11	5	78	77	3	15	5	142	131	-5	1	6	127	119	0	4	6	238	219	3	7	6	75	79
-1	11	5	89	80	4	15	5	105	-99	-4	1	6	157	167	4	4	6	81	-82	4	7	6	178	156
0	11	5	73	-71	6	15	5	70	75	-3	1	6	117	-106	5	4	6	119	116	-6	8	6	139	-149
1	11	5	231	231	-3	16	5	75	68	-2	1	6	110	86	-6	5	6	35	-38	-5	8	6	317	295
3	11	5	155	-152	1	16	5	78	105	-1	1	6	264	-293	-5	5	6	191	-189	-4	8	6	55	-55
6	11	5	72	-71	3	16	5	91	78	1	1	6	188	194	-4	5	6	131	-130	-2	8	6	76	-96
-6	12	5	98	-96	-4	17	5	127	122	2	1	6	332	-313	-3	5	6	150	119	-1	8	6	343	322
-4	12	5	199	203	-1	17	5	229	219	4	1	6	105	106	-2	5	6	321	-338	0	8	6	328	-291
-3	12	5	341	-332	0	17	5	125	-109	5	1	6	83	-86	-1	5	6	244	236	1	8	6	455	-478
-2	12	5	165	-151	1	17	5	125	-122	-5	2	6	63	-52	0	5	6	219	-204	2	8	6	306	301

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
3	8	6	168	186	-6	12	6	78	87	3	16	6	145	-144	-1	3	7	78	98	0	7	7	387	350
4	8	6	193	-185	-4	12	6	112	105	4	16	6	107	105	0	3	7	77	81	1	7	7	436	389
5	8	6	94	98	-3	12	6	140	-141	-3	17	6	111	91	1	3	7	344	-324	2	7	7	241	-252
-5	9	6	182	181	0	12	6	135	159	-2	17	6	79	-86	2	3	7	146	129	3	7	7	223	-223
-4	9	6	116	113	1	12	6	116	-116	0	17	6	166	152	4	3	7	142	-148	4	7	7	56	59
-3	9	6	269	-226	2	12	6	135	-120	1	17	6	93	34	-5	4	7	47	41	5	7	7	177	198
-2	9	6	102	168	3	12	6	90	88	-5	18	6	81	-75	-4	4	7	356	-358	6	7	7	106	-132
-1	9	6	165	-166	4	12	6	98	91	-4	18	6	34	-38	-3	4	7	296	-284	-5	8	7	66	70
0	9	6	114	109	5	12	6	114	-110	-3	18	6	119	105	-2	4	7	667	696	-4	8	7	54	-46
2	9	6	145	152	-4	13	6	180	-177	-1	18	6	121	-118	-1	4	7	173	-157	-3	8	7	286	279
3	9	6	77	87	-3	13	6	156	-152	1	18	6	63	56	1	4	7	228	-232	-2	8	7	146	-122
5	9	6	258	252	-2	13	6	155	161	4	18	6	67	46	2	4	7	408	424	-1	8	7	157	153
-6	10	6	124	-123	-1	13	6	165	-158	-1	20	6	73	80	3	4	7	366	-370	0	8	7	94	121
-5	10	6	79	87	1	13	6	140	156	-6	1	7	65	-70	-4	5	7	246	-246	2	8	7	245	249
-4	10	6	143	150	4	13	6	99	-108	-5	1	7	47	54	-3	5	7	360	-371	3	8	7	236	240
-3	10	6	64	-57	6	13	6	55	-50	-4	1	7	253	272	-2	5	7	198	220	4	8	7	216	-216
-2	10	6	117	99	-5	14	6	93	-103	-3	1	7	127	-126	-1	5	7	119	-136	-6	9	7	134	137
-1	10	6	192	191	-4	14	6	125	-129	-2	1	7	209	-187	0	5	7	329	-320	-5	9	7	136	-140
0	10	6	225	-224	-3	14	6	132	144	-1	1	7	571	563	1	5	7	249	262	-3	9	7	138	135
1	10	6	347	-339	-2	14	6	229	-246	0	1	7	106	-117	2	5	7	75	61	-2	9	7	116	125
3	10	6	107	-110	-1	14	6	88	-84	1	1	7	140	-143	4	5	7	129	-123	-1	9	7	296	-289
4	10	6	191	-198	0	14	6	102	79	4	1	7	76	-75	5	5	7	63	62	2	9	7	168	-152
6	10	6	67	74	1	14	6	156	148	6	1	7	159	164	-5	6	7	202	202	4	9	7	456	466
-6	11	6	72	-69	5	14	6	95	93	-5	2	7	166	147	-3	6	7	268	-259	5	9	7	64	72
-5	11	6	66	-66	-6	15	6	96	94	-4	2	7	353	-356	-2	6	7	85	100	6	9	7	116	-113
-4	11	6	48	-50	-5	15	6	61	62	-3	2	7	205	196	0	6	7	159	-165	-4	10	7	129	126
-3	11	6	144	-134	-2	15	6	120	117	-2	2	7	77	-67	1	6	7	64	-57	-3	10	7	230	-267
-2	11	6	145	145	-1	15	6	73	79	0	2	7	221	-235	5	6	7	124	130	-1	10	7	80	-97
0	11	6	248	-221	0	15	6	95	-78	1	2	7	136	160	-6	7	7	54	56	2	10	7	198	-194
2	11	6	178	159	-3	16	6	125	126	2	2	7	243	236	-5	7	7	139	-151	4	10	7	195	209
3	11	6	130	-151	-2	16	6	143	125	4	2	7	46	43	-4	7	7	46	34	5	10	7	76	-73
4	11	6	104	-155	-1	16	6	203	-202	-4	3	7	85	87	-3	7	7	126	137	-3	11	7	187	202
5	11	6	133	144	1	16	6	203	218	-3	3	7	53	39	-2	7	7	138	-134	-2	11	7	116	102
6	11	6	57	58	2	16	6	81	-64	-2	3	7	228	205	-1	7	7	507	-493	-1	11	7	86	-82

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
1	11	7	83	-90	-3	17	7	64	-44	-6	3	8	121	-116	-4	7	8	64	76	6	10	8	60	62
4	11	7	135	-156	0	17	7	192	-169	-5	3	8	96	-101	-3	7	8	84	-9	-2	11	8	291	276
-6	12	7	73	-79	1	17	7	168	-141	-3	3	8	87	92	-2	7	8	120	112	-1	11	8	121	110
-5	12	7	242	-232	-4	18	7	101	-98	-2	3	8	260	-243	-1	7	8	68	-74	0	11	8	138	-130
-3	12	7	268	266	-1	18	7	109	107	-1	3	8	166	174	0	7	8	86	97	1	11	8	99	107
-2	12	7	128	-119	2	18	7	86	71	0	3	8	463	442	1	7	8	57	-71	2	11	8	164	158
0	12	7	283	287	-2	19	7	70	-72	2	3	8	152	-142	2	7	8	92	-87	4	11	8	277	-273
2	12	7	244	-235	1	19	7	81	-85	4	3	8	233	229	3	7	8	311	-326	-4	12	8	100	-108
3	12	7	94	102	-3	20	7	59	-67	-4	4	8	298	296	4	7	8	175	179	-3	12	8	283	295
4	12	7	91	-96	-2	20	7	108	99	-3	4	8	49	-60	6	7	8	76	-78	-2	12	8	115	-126
5	12	7	54	47	0	20	7	83	-80	-2	4	8	300	-270	-6	8	8	174	-180	2	12	8	77	-83
-6	13	7	56	-53	-5	0	8	123	-105	-1	4	8	585	-550	-5	8	8	54	48	3	12	8	88	-77
-5	13	7	91	97	-4	0	8	401	-380	0	4	8	311	-306	-4	8	8	293	297	-6	13	8	52	55
-4	13	7	73	65	-3	0	8	150	165	1	4	8	133	116	-3	8	8	626	-622	-4	13	8	52	-62
-3	13	7	174	-193	-2	0	8	383	421	5	4	8	58	65	-2	8	8	226	227	-3	13	8	133	-144
-2	13	7	82	-82	-1	0	8	669	595	-6	5	8	141	-136	-1	8	8	295	272	-2	13	8	93	78
-1	13	7	130	161	1	0	8	544	525	-5	5	8	110	90	0	8	8	170	-159	0	13	8	152	-132
1	13	7	78	79	4	0	8	148	182	-3	5	8	491	492	1	8	8	408	-411	2	13	8	228	228
2	13	7	124	110	6	0	8	156	-147	-2	5	8	487	-499	2	8	8	167	160	5	13	8	92	96
3	13	7	73	-71	-6	1	8	150	157	-1	5	8	367	-331	-6	9	8	100	100	1	14	8	195	200
-6	14	7	53	-45	-5	1	8	192	-175	0	5	8	467	497	-5	9	8	61	65	5	14	8	60	-55
-5	14	7	57	-68	-4	1	8	133	-140	1	5	8	126	-125	-4	9	8	84	-84	-5	15	8	64	75
-4	14	7	140	145	-3	1	8	60	-35	2	5	8	103	-96	-3	9	8	84	-85	-4	15	8	136	-131
-2	14	7	190	-150	-2	1	8	269	-277	4	5	8	271	281	-1	9	8	175	175	-3	15	8	92	-64
-1	14	7	149	-128	-1	1	8	532	-614	5	5	8	68	77	0	9	8	131	-122	-1	15	8	129	-126
2	14	7	103	-82	0	1	8	134	149	-6	6	8	47	51	1	9	8	92	-96	0	15	8	119	-106
3	14	7	70	59	1	1	8	134	-130	-5	6	8	64	64	4	9	8	184	-188	5	15	8	59	61
-2	15	7	90	-70	2	1	8	169	181	-2	6	8	83	83	-6	10	8	136	-135	-6	16	8	98	119
-1	15	7	235	246	-6	2	8	100	101	-1	6	8	186	-183	-4	10	8	89	82	-5	16	8	59	51
1	15	7	73	-64	-4	2	8	186	-196	0	6	8	92	91	-3	10	8	133	-140	-4	16	8	107	-99
2	15	7	87	76	-3	2	8	141	142	1	6	8	395	-378	-2	10	8	93	-93	-3	16	8	97	94
4	16	7	36	52	-2	2	8	126	107	4	6	8	294	-300	-1	10	8	165	151	-1	16	8	63	-63
5	16	7	64	-74	0	2	8	104	150	5	6	8	60	-60	0	10	8	152	164	0	16	8	136	-136
-4	17	7	30	-52	1	2	8	107	113	-6	7	8	79	-77	2	10	8	94	94	-4	13	8	89	-81

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
0	18	8	93	-85	0	4	9	351	-330	-6	9	9	104	114	-3	14	9	83	72	6	1	10	61	-61
1	18	8	89	91	2	4	9	219	230	-5	9	9	80	-83	-2	14	9	61	-51	-6	2	10	79	32
-3	19	8	108	89	4	4	9	114	-120	-4	9	9	364	-379	0	14	9	123	124	-4	2	10	99	-126
-2	19	8	57	-59	5	4	9	118	130	-3	9	9	315	336	2	14	9	85	-63	-3	2	10	88	35
0	19	8	143	127	-3	5	9	155	-171	-2	9	9	342	344	4	14	9	81	82	-2	2	10	122	-133
2	19	8	49	-43	-2	5	9	198	205	-1	9	9	248	-273	-3	15	9	86	-69	-1	2	10	215	-233
-6	1	9	57	-69	-1	5	9	206	-220	1	9	9	255	273	-2	15	9	150	-135	0	2	10	107	-39
-4	1	9	68	70	2	5	9	262	266	2	9	9	137	-148	-1	15	9	110	127	1	2	10	117	118
-1	1	9	399	400	4	5	9	170	-166	5	9	9	56	54	1	15	9	72	-64	2	2	10	287	282
0	1	9	372	347	-5	6	9	117	116	6	9	9	59	-60	4	15	9	39	-40	4	2	10	120	116
1	1	9	296	-306	-4	6	9	169	-170	-4	10	9	195	-182	-4	16	9	53	-42	-6	3	10	135	154
4	1	9	114	114	-3	6	9	91	-78	-2	10	9	140	-148	-2	16	9	61	-48	-5	3	10	102	-87
6	1	9	88	92	-1	6	9	78	66	-1	10	9	153	-144	-1	16	9	84	-70	-3	3	10	251	252
-5	2	9	163	156	1	6	9	191	-182	0	10	9	127	120	-4	17	9	56	55	-2	3	10	151	155
-4	2	9	96	-107	2	6	9	149	151	2	10	9	89	-77	-3	17	9	46	-38	-1	3	10	278	-255
-2	2	9	297	323	4	6	9	135	133	6	10	9	64	-69	-1	17	9	161	159	0	3	10	351	358
-1	2	9	232	-233	5	6	9	66	73	-6	11	9	65	75	1	17	9	136	-118	1	3	10	87	-36
0	2	9	165	-172	-6	7	9	93	99	-4	11	9	159	165	2	17	9	62	54	2	3	10	180	-182
1	2	9	87	70	-4	7	9	127	-117	-3	11	9	133	-150	-4	18	9	108	-7	-6	4	10	80	-63
2	2	9	287	269	-3	7	9	71	67	-1	11	9	79	-60	-3	18	9	65	-50	-5	4	10	194	187
4	2	9	283	-296	-2	7	9	245	267	0	11	9	132	-128	-1	18	9	56	-64	-4	4	10	140	-125
-6	3	9	126	-131	0	7	9	91	-51	2	11	9	89	89	0	18	9	127	-107	-2	4	10	170	164
-5	3	9	113	102	1	7	9	148	150	4	11	9	176	170	-5	0	10	67	54	-1	4	10	84	67
-4	3	9	112	128	3	7	9	325	-369	5	11	9	120	115	-4	0	10	224	-262	0	4	10	198	139
-3	3	9	86	-71	5	7	9	98	98	-5	12	9	80	-70	-3	0	10	293	278	-5	5	10	176	-161
-2	3	9	392	-425	6	7	9	82	-75	-4	12	9	119	107	-2	0	10	327	326	-4	5	10	311	323
-1	3	9	187	-210	-6	8	9	139	-145	-3	12	9	152	151	-1	0	10	312	-269	-3	5	10	95	132
1	3	9	55	-53	-5	8	9	139	-144	-2	12	9	93	81	1	0	10	119	113	-1	5	10	281	-290
2	3	9	176	-182	-4	8	9	173	174	-1	12	9	167	158	2	0	10	315	-309	0	5	10	172	164
6	3	9	57	-59	-3	8	9	58	-28	2	12	9	162	-136	-4	1	10	76	-83	2	5	10	167	169
-5	4	9	284	281	-2	8	9	172	-179	4	12	9	77	74	-3	1	10	82	80	4	5	10	134	129
-4	4	9	64	-72	0	8	9	118	118	5	12	9	100	-99	-2	1	10	214	-186	-6	6	10	75	-74
-2	4	9	267	269	1	8	9	84	92	-6	13	9	57	-62	1	1	10	148	150	-5	6	10	132	-118
-1	4	9	249	264	2	8	9	108	101	-2	13	9	196	-191	4	1	10	130	147	-4	6	10	84	77

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-3	6	10	86	-112	-3	10	10	160	-178	-3	1	11	49	51	1	6	11	145	-146	1	11	11	123	123
-2	6	10	87	-65	-2	10	10	159	-137	-2	1	11	248	-249	2	6	11	183	185	4	11	11	73	-79
0	6	10	173	-175	-1	10	10	173	180	-1	1	11	111	135	4	6	11	98	-103	-6	12	11	76	83
1	6	10	113	-109	0	10	10	203	191	0	1	11	108	114	-6	7	11	83	87	-5	12	11	62	-59
2	6	10	85	-73	1	10	10	83	-83	1	1	11	216	-234	-5	7	11	155	157	-3	12	11	93	99
4	6	10	106	-103	-5	11	10	63	58	4	1	11	45	-52	-4	7	11	137	-126	-2	12	11	163	-147
5	6	10	97	-99	-3	11	10	59	-39	-6	2	11	54	-57	-3	7	11	281	-277	-1	12	11	85	-80
-6	7	10	71	-73	-2	11	10	221	-211	-4	2	11	58	-66	-2	7	11	70	61	0	12	11	115	92
-4	7	10	249	-274	-3	12	10	61	59	-3	2	11	439	-457	-1	7	11	216	-217	1	12	11	78	68
-3	7	10	138	175	-2	12	10	70	51	-2	2	11	136	148	2	7	11	165	-166	2	12	11	76	-62
-2	7	10	118	116	-1	12	10	127	-136	-1	2	11	273	259	4	7	11	109	115	4	12	11	115	104
1	7	10	149	183	0	12	10	120	-132	1	2	11	229	-243	6	7	11	36	-45	-6	13	11	85	-69
2	7	10	99	-77	4	12	10	93	88	2	2	11	470	478	-4	8	11	90	82	-4	13	11	131	131
4	7	10	73	-82	-5	13	10	217	219	6	2	11	98	111	-3	8	11	107	105	-3	13	11	141	121
-6	8	10	83	-85	-2	13	10	233	211	-5	3	11	146	-153	-2	8	11	104	-103	-1	13	11	140	144
-5	8	10	91	-96	-1	13	10	130	134	-3	3	11	137	156	-1	8	11	134	-141	-5	14	11	98	-95
-4	8	10	265	278	0	13	10	227	-235	0	3	11	82	76	1	8	11	99	-94	-3	14	11	151	126
-3	8	10	117	-104	2	13	10	83	69	-6	4	11	81	-86	2	8	11	312	-296	0	14	11	142	121
-2	8	10	130	-98	4	13	10	82	-80	-5	4	11	318	326	6	8	11	40	50	1	14	11	94	92
-1	8	10	266	248	-4	14	10	50	-39	-4	4	11	100	-86	-6	9	11	100	101	4	14	11	30	28
0	8	10	140	141	-3	14	10	117	121	-3	4	11	320	-323	-5	9	11	99	-98	-2	15	11	138	-110
1	8	10	215	-219	-2	14	10	77	45	-2	4	11	216	190	-2	9	11	138	129	-1	15	11	96	-103
2	8	10	116	-117	-1	14	10	139	-137	-1	4	11	242	248	-1	9	11	78	-81	0	15	11	103	84
4	8	10	204	-203	1	14	10	59	69	0	4	11	126	-107	1	9	11	145	152	1	15	11	104	-93
6	8	10	83	81	-3	15	10	100	-90	2	4	11	243	234	4	9	11	57	-52	-2	16	11	123	95
-4	9	10	49	-47	-2	15	10	76	58	-4	5	11	123	123	-5	10	11	81	-68	1	16	11	72	79
-3	9	10	164	-157	-1	15	10	225	206	-3	5	11	131	131	-2	10	11	117	-113	-4	17	11	38	45
-2	9	10	263	-257	1	16	10	116	110	-1	5	11	116	139	0	10	11	121	-131	-3	17	11	41	-41
-1	9	10	167	171	-1	17	10	77	-86	2	5	11	143	133	1	10	11	187	208	-2	17	11	114	-93
0	9	10	101	-109	0	18	10	73	72	-6	6	11	52	49	2	10	11	83	-77	-1	17	11	86	95
1	9	10	86	-101	-1	19	10	138	-137	-3	6	11	160	135	4	10	11	136	141	-6	0	12	237	213
4	9	10	102	122	-6	1	11	159	-136	-2	6	11	83	81	-4	11	11	172	-169	-4	0	12	266	-292
-6	10	10	67	65	-5	1	11	152	160	-1	6	11	89	84	-2	11	11	164	162	-2	0	12	73	51
-5	10	10	120	110	-4	1	11	89	-102	0	6	11	107	-113	0	11	11	103	-90	-1	0	12	113	-78

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
0	0	12	155	-157	4	5	12	39	53	-3	13	12	98	-86	-3	4	13	300	-320	-3	10	13	178	175
1	0	12	160	-190	-4	6	12	161	166	-1	13	12	75	83	-1	4	13	77	46	-2	10	13	119	99
2	0	12	387	379	-3	6	12	159	135	0	13	12	153	-149	1	4	13	300	-280	1	10	13	127	125
-3	1	12	63	68	-2	6	12	147	-132	1	13	12	93	-97	-4	5	13	95	84	4	10	13	57	33
-2	1	12	368	386	-1	6	12	72	-52	2	13	12	57	45	-3	5	13	119	108	-3	11	13	95	-84
-1	1	12	104	98	0	6	12	148	151	4	13	12	69	-44	-1	5	13	113	133	-2	11	13	94	-133
2	1	12	48	-42	1	6	12	66	-60	-4	14	12	64	-73	0	5	13	124	-124	-1	11	13	86	59
4	1	12	146	156	4	6	12	142	144	-2	14	12	103	143	2	5	13	223	-219	0	11	13	98	-81
-6	2	12	43	-40	-6	7	12	81	86	0	14	12	244	-223	4	5	13	51	65	1	11	13	91	-112
-5	2	12	80	88	-5	7	12	83	-95	2	14	12	130	104	-6	6	13	82	-82	4	11	13	66	-59
-4	2	12	188	-190	-4	7	12	68	59	-3	15	12	53	-61	-3	6	13	162	-176	-6	12	13	62	51
-3	2	12	136	-122	-3	7	12	67	-73	-1	15	12	96	73	-2	6	13	135	152	-4	12	13	147	-143
-1	2	12	102	-129	0	7	12	115	-132	1	15	12	110	-89	4	6	13	139	-132	-1	12	13	86	-73
0	2	12	160	-171	-6	8	12	120	-121	2	15	12	69	-47	-6	7	13	111	119	-3	13	13	73	-76
1	2	12	180	192	-4	8	12	96	83	-4	16	12	101	-103	-5	7	13	105	-97	-1	13	13	76	-83
2	2	12	105	113	-2	8	12	360	-354	-3	16	12	66	-67	-4	7	13	112	-114	1	13	13	152	-147
-6	3	12	80	82	-1	8	12	83	90	-2	16	12	65	57	-3	7	13	71	69	2	13	13	145	-132
-5	3	12	161	-158	2	8	12	217	-203	-2	17	12	56	-57	-2	7	13	111	83	-1	14	13	72	-63
-3	3	12	194	171	-3	9	12	180	185	-6	1	13	54	-60	0	7	13	201	-187	2	14	13	75	-79
-2	3	12	105	-120	-2	9	12	192	172	-4	1	13	69	78	1	7	13	203	218	-4	15	13	66	63
-1	3	12	145	-121	2	9	12	86	67	-3	1	13	237	-255	2	7	13	206	177	0	15	13	92	97
0	3	12	56	-58	-4	10	12	76	78	-2	1	13	387	-200	4	7	13	73	-72	-5	0	14	228	218
-6	4	12	41	55	-3	10	12	127	-132	0	1	13	104	100	-6	8	13	44	48	-4	0	14	76	92
-3	4	12	153	179	-2	10	12	196	-188	1	1	13	96	-107	-2	8	13	73	-75	-3	0	14	145	132
-2	4	12	240	253	0	10	12	113	90	-6	2	13	67	-72	-1	8	13	87	92	-1	0	14	139	-113
-1	4	12	228	244	1	10	12	65	-82	-5	2	13	123	118	4	8	13	56	52	1	0	14	188	225
2	4	12	87	-79	2	10	12	118	-105	-4	2	13	376	376	-5	9	13	98	95	-6	1	14	84	97
6	4	12	80	-73	-3	11	12	78	-65	-2	2	13	137	-122	-4	9	13	81	-77	-3	1	14	118	132
-5	5	12	64	-66	-1	11	12	102	109	-1	2	13	163	175	-2	9	13	152	158	-2	1	14	193	188
-2	5	12	207	-207	1	11	12	75	96	-4	3	13	54	-56	-1	9	13	89	-93	-1	1	14	114	-139
-1	5	12	134	-148	2	11	12	95	78	-3	3	13	220	252	0	9	13	121	-107	1	1	14	128	-173
0	5	12	169	142	-2	12	12	139	142	0	3	13	186	162	1	9	13	281	305	2	1	14	86	-94
1	5	12	89	71	-1	12	12	94	-106	1	3	13	133	-128	4	9	13	54	-48	-1	2	14	84	73
2	5	12	394	-393	-4	13	12	55	58	-4	4	13	180	193	-4	10	13	51	63	1	2	14	91	-104

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-5	3	14	88	-86	-4	9	14	91	98	-4	5	15	189	-174	-3	0	16	112	-113	-6	3	17	76	87
-4	3	14	52	56	-1	9	14	72	69	-3	5	15	100	-101	-2	0	16	133	109	-1	3	17	118	-115
-2	3	14	80	58	0	9	14	117	-109	-4	6	15	105	109	-1	0	16	145	-180	0	3	17	126	114
-1	3	14	266	-283	-4	10	14	70	74	-1	6	15	102	116	-5	1	16	64	-64	-6	4	17	64	-61
1	3	14	241	280	-3	10	14	60	59	-5	7	15	108	93	0	1	16	285	-286	-4	4	17	98	36
2	3	14	214	-200	1	10	14	75	-81	-4	7	15	46	-44	1	1	16	148	178	-3	4	17	75	94
4	3	14	90	100	2	10	14	153	-147	-3	7	15	79	-75	-3	2	16	64	-57	-1	4	17	106	113
-6	4	14	40	48	-5	11	14	127	117	-2	7	15	137	132	-2	2	16	175	214	-3	5	17	125	-117
-5	4	14	132	-132	-3	11	14	102	-110	-1	7	15	170	166	-6	3	16	92	97	-1	5	17	128	121
-4	4	14	103	-117	-1	11	14	128	119	0	7	15	210	-207	-4	3	16	168	-164	-5	6	17	82	75
-3	4	14	170	-181	1	11	14	119	-104	2	7	15	136	119	-1	3	16	144	-169	-4	6	17	58	43
-1	4	14	74	86	-4	12	14	100	-31	-6	8	15	50	52	1	3	16	127	134	-3	6	17	74	-83
0	4	14	193	-192	-1	12	14	68	71	-3	8	15	79	-77	-6	4	16	43	-42	-2	6	17	81	-46
-5	5	14	201	-204	1	12	14	64	-69	2	8	15	106	93	-2	4	16	112	-110	1	6	17	110	-127
-3	5	14	196	214	-3	13	14	109	-93	-6	9	15	55	59	-6	5	16	112	107	-6	7	17	52	-74
0	5	14	141	148	-3	15	14	40	42	-5	9	15	162	147	-2	5	16	139	146	-2	7	17	65	52
1	5	14	138	140	-1	15	14	52	58	-2	9	15	58	-56	-1	5	16	91	-72	1	7	17	83	-76
2	5	14	82	-82	1	15	14	54	-35	0	9	15	180	-169	-3	6	16	87	83	-4	8	17	47	-45
-6	6	14	53	-62	-5	1	15	59	-54	2	9	15	90	68	-2	6	16	95	-94	-3	8	17	63	-51
-2	6	14	82	-97	-4	1	15	223	238	-5	10	15	83	66	2	6	16	151	-142	-3	9	17	58	-67
0	6	14	112	65	-2	1	15	91	-85	-2	10	15	57	40	-5	9	16	57	-56	-4	10	17	82	-76
1	6	14	181	189	0	1	15	190	193	-1	10	15	89	-88	-4	9	16	39	30	-6	11	17	59	55
4	6	14	80	81	-2	2	15	187	-185	2	10	15	94	-84	-3	10	16	121	128	-2	11	17	45	-36
-6	7	14	60	-66	1	2	15	177	-195	-4	11	15	65	76	-2	10	16	99	-91	-1	12	17	64	-67
-3	7	14	84	-101	-6	3	15	69	-61	-2	11	15	88	77	-4	11	16	58	45	-3	0	18	129	-123
-2	7	14	86	82	-5	3	15	119	-117	-5	12	15	94	-89	1	11	16	113	-106	-2	0	18	90	92
-1	7	14	138	-159	-1	3	15	100	-92	-3	12	15	56	41	0	12	16	96	96	-6	1	18	36	-49
2	7	14	67	67	1	3	15	116	152	-1	12	15	91	-88	-3	13	16	38	-37	-4	1	18	59	-59
-5	8	14	112	-116	2	3	15	122	-113	-4	13	15	80	-85	-1	13	16	67	79	-1	1	18	113	-16
-4	8	14	131	113	-6	4	15	107	-115	0	13	15	114	103	-5	1	17	109	-107	-2	2	18	49	33
-3	8	14	145	140	-3	4	15	92	-82	-2	14	15	81	38	-1	1	17	65	-70	0	2	18	96	-76
-2	8	14	124	-110	-1	4	15	75	34	-1	14	15	65	-68	-4	2	17	63	44	-5	3	18	64	57
0	8	14	207	190	0	4	15	142	-147	-6	0	16	47	35	0	2	17	163	153	-3	3	18	68	78
-5	9	14	94	84	-6	5	15	53	57	-4	0	16	50	-42	1	2	17	83	-75	-2	3	18	66	56

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 11870

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
-1	3	18	142	141	-1	6	18	92	-94	-2	10	18	48	55	-4	4	19	51	48	-3	8	19	74	75
0	4	18	67	68	0	6	18	69	71	-3	1	19	67	56	-2	4	19	74	-51	-4	0	20	86	-85
-4	5	18	76	-97	-1	7	18	54	-52	-2	1	19	56	50	-2	6	19	114	-122	0	0	20	85	-104
-3	5	18	59	51	-3	8	18	85	69	-4	2	19	72	-60	-3	7	19	71	-60	-2	1	20	167	-53
-1	5	18	78	-79	-2	8	18	67	-70	1	3	19	66	63	0	7	19	73	-75	-2	3	20	61	65
1	5	18	106	96	-2	9	18	52	-35															

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